Crimean-Congo Hemorrhagic Fever Virus

Subjects: Infectious Diseases

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Crimean-Congo hemorrhagic fever virus (CCHFV) is a widespread, tick-borne pathogen that causes Crimean-Congo hemorrhagic fever (CCHF) with high morbidity and mortality. CCHFV is transmitted to humans through tick bites or direct contact with patients or infected animals with viremia. Currently, climate change and globalization have increased the transmission risk of this biosafety level (BSL)-4 virus.

Keywords: Crimean-Congo hemorrhagic fever virus ; bunyavirus ; tick-borne virus ; antiviral strategies

1. Introduction

The virus is transmitted to humans by the bites of infected ticks of theHyalommagenus, or direct contact with tissue or body fluids from infected animals and humans [1]. A large variety of animals, such as cattle, donkeys, goats, hares, horses, ostriches, small rodents, and sheep, develop viremia without noticeable symptoms of illness following CCHFV infection [2], despite its high pathogenicity in humans. Following viral challenge, newborn mice, a subset of immunocompromised rodents and cynomolgus macaques could partially recapitulate the human disease and have been assessed as potential animal models of CCHFV [2][3][4]. The limits of appropriate animal models, as well as the requirement of such a biosafety level (BSL)-4 virus for high-containment laboratories, largely slow down the progress in virological study and development of antiviral drugs and vaccines.

CCHFV belongs to the genus *Orthonairovirus*, family *Nairoviridae*, order *Bunyavirales*[5]. The viral genome is composed of three negative-sense RNA segments. The small (S) segment encodes the nucleoprotein (NP) , the medium (M) segment encodes the glycoprotein precursor (GPC) that is subsequently cleaved into mature Gn, Gc, and several nonstructural proteins including mucin, GP38 and NSm, and the large (L) segment encodes the L protein which contains the RNA-dependent RNA polymerase (RdRp) catalyzing viral RNA synthesis and an ovarian tumor (OTU) protease domain likely involved in viral antagonism of host innate immunity [6][7][8].

Due to the lack of specific antiviral therapies, high mortality rate, increased vector bionomics and climate change, CCHFV is considered an emerging arboviral zoonotic disease in many countries and is listed as a highly infectious pathogen that could cause a public health emergency. Thus, the development of novel antiviral therapeutics against CCHFV is urgently needed to manage the increasing public health threat of CCHF. Ribavirin, a broad-spectrum antiviral medication, has been administered to human cases of CCHF; however, the therapeutic benefits remain elusive [9]. In addition, potential inhibitors of bunyaviruses have been evaluated over the past decades and some of them have demonstrated possible efficacy to CCHFV infection.

2. Current Antiviral Strategies

Nucleoside analogues, a class of drugs targeting viral RNA polymerase, exhibit broad-spectrum antiviral activity against many distinct viruses both in vitro and in vivo. Many of them are currently being evaluated as candidate drugs for therapeutic use in emerging infections [10][11]. Several, including ribavirin, favipiravir and 2′-deoxy-2′-fluorocytidine, have also been used in anti-CCHFV tests.

In 1989, Watts et al. reported the anti-CCHFV effectiveness of ribavirin by in vitro tests with African green monkey kidney cell line (Vero cells), in which the drug significantly decreased the replication of various CCHFV strains [12]. The protective activity of ribavirin was then examined in CCHFV-infected suckling mice [13] and signal transducer and activator of transcription-1 (STAT-1) deficient mice. However, clinical evidence for the beneficial treatment of ribavirin is inconsistent and has attracted debate among researchers and clinicians [9][14]. Systematic reviews and meta-analyses showed insufficient efficacy of ribavirin for CCHF patients [15], or suggested that early treatment with ribavirin, <48 h after symptom onset, was needed for clinical benefit [16].

Favipiravir (also known as T-705) is licensed in Japan for the treatment of influenza virus infections but has shown promise against other highly pathogenic RNA viruses including severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), Hantavirus, and Rift Valley fever virus (RVFV), as well as CCHFV [11][17][18]. Two groups have evaluated favipiravir against CCHFV in a type I interferon-deficient mouse model and both showed that favipiravir treatment effectively suppresses viral replication in several tissues and can reduce mortality following diverse CCHFV strain infections [19][20]. has shown that favipiravir treatment is efficacious in inhibiting viral replication and preventing a lethal outcome following CCHFV infection, even when treatment is started two days before the expected time of death [20]. However, compared to the results from the mouse model, favipiravir treatment only showed a modest benefit in CCHFV-infected cynomolgus macaques, even though treatment was initiated 24 h post-infection, which may be attributed to the subcutaneous administration of favipiravir and nonuniform lethality of the cynomolgus macaque model [21] and needs further investigation to be clarified.

In addition to ribavirin and favipiravir mentioned above, several other prominent broad-spectrum inhibitors against bunyavirus infections also have been reported. They identified a compound, 2′-deoxy-2′-fluorocytidine (also known as 2′-fluoro-2′-deoxycytidin, 2′-dFC) as a potential CCHFV antiviral, with inhibitory activity superior to that of favipiravir or ribavirin in vitro. They also demonstrated that 2′-dFC acts synergistically with favipiravir to inhibit CCHFV replication without causing cytotoxicity, suggesting the potential of a combination therapy with 2′-dFC and favipiravir [22]. They indicated that 2′-FdC has inhibitory effectiveness against both RVFV and severe fever with thrombocytopenia syndrome virus (SFTSV) and is thus a promising candidate for treating certain bunyavirus infections [23].

Many viruses encode deubiquitinating (DUB) enzymes that play an important role in viral replication and innate immune evasion. The CCHFV L protein contains an OTU domain also exhibiting DUB activity, which binds and removes ubiquitin (Ub) and This makes the DUB active site of CCHFV OTU a highly attractive drug target, as disrupting the activity is expected to not only directly interfere with viral replication but also enhance immune responses upon infection. Kocabas and Aslan developed a fluorescent reporter assay of CCHFV OTU protease to screen CCHFV OTU inhibitors that might possess potential antiviral activity against CCHFV.

The innate immune response is the first line of host defense against viral infections in mammalian cells [24][25]. Previous studies have shown that CCHFV infection results in the substantial secretion of type I interferons (IFNs), especially IFN-α and IFN-β, and subsequent upregulation of interferon-stimulated genes (ISGs) [26][27]. However, established CCHFV infection is almost insensitive to subsequent treatment with IFN-α and moreover, no positive clinical data is available on IFN use against CCHF by far [28][29]. Recently, Bordi et al. demonstrated that type III IFN (IFN-λ1) also has an anti-CCHFV activity, although it seems to be less effective compared with type I IFN (IFN-α).

With antibody engineering advancing, antibody therapy has been growing steadily in recent years. Antibodies, especially monoclonal antibodies (mAbs), have been demonstrated to be effective in the treatment of several hemorrhagic fever virus-related infectious diseases with in vitro and in vivo models, including those caused by Ebola and Lassa viruses [30] [31].

Vaccine studies in mice have shown that antibodies play an important role in preventing CCHFV infection [32][33]. However, the effectiveness of convalescent serum has not been evaluated in randomized controlled clinical trials with large sample sizes and no studies have proven the efficacy of specific immunoglobulin for the post-exposure prophylaxis or treatment of CCHF [34]. Moreover, there are still a number of challenges that prevent the large-scale adoption of convalescent serum, such as limited sources, individual differences and the complexity of blood products. Therefore, serum or immunoglobulin from convalescent patients is usually used in emergencies.

However, only a subset of Gc mAbs exhibited a protective effect in mice after passive immunization, whereas some non-neutralizing Gn mAbs protected suckling mice from a lethal challenge with the CCHFV strain IbAr10200, suggesting that antibody activities against CCHFV depend not only on the neutralizing properties, but also on host factors and non-neutralizing antibody-dependent mechanisms [35]. They demonstrated that, interestingly, a non-neutralizing antibody actually binding to GP38 (a secreted nonstructural glycoprotein in CCHFV), 13G8, protects the mouse model against lethal CCHFV infection [36]. Strategies, e.g., antibody cocktail therapy and antibody–drug coupling, which can improve the biological activity of antibodies, will enhance the efficacy of antibody therapy. To generate antibodies with increased antiviral activity and limited risk to induce viral escape mutation, they engineered bispecific antibodies bearing variable domains from two antibodies with a synergistic effect and successfully identified one antibody, DVD-121-801, that affords both prophylactic and therapeutic potential against CCHFV challenge in IFNAR−/−mice [37].

Although antibody treatment for CCHF remains in its infancy, this approach may be an effective therapy against CCHFV in the absence of approved drugs.

Targeting host cell pathways supporting viral replication is an attractive approach for the development of antiviral intervention strategies. Ferraris et al. investigated the anti-CCHFV activity of FDA-approved molecules targeting endocytic pathways. In their in vitro antiviral testing, chloroquine and chlorpromazine that interfere with the clathrin/pH-dependent endocytic pathway were identified as potential antiviral drugs for CCHFV [38]. Chloroquine or chlorpromazine and ribavirin combination assays demonstrated synergistic effects, suggesting that combinatorial treatment may be a better strategy to control CCHFV infection.

Tampere et al. established an image-based phenotypic high-throughput screening assay coupled with automated image analysis and tested a set of in-house small molecule inhibitors targeting oxidative stress and nucleotide metabolism pathways. The newly identified antiviral molecules, TH3289 and TH6744, exhibited broad antiviral activity against emerging RNA viruses including SARS-CoV-2, Ebola virus (EBOV), Hazara virus, as well as CCHFV, likely due to its multifaceted effects on cellular heat shock protein 70 (HSP70) pathways [39].

RNA interference using small interfering RNAs (siRNAs) to silence genes might be used to regulate viral replication by targeting cellular processes such as those aforementioned or directly by targeting viral genes. Foldes et al. designed chemically synthesized siRNAs targeting viral genes that could inhibit CCHFV replication in vitro [40]. Therein, they identified effective siRNAs targeting all the three segments of the CCHFV genome, providing support for the potential use of RNA interference techniques in the rational design of anti-CCHFV drugs.

3. Conclusions and Prospects

CCHF is a medically important tick-borne viral disease of humans with wide prevalence and is listed by the WHO as one of the top priority diseases for research and development in public health emergency contexts (https://www.who.int/activities/prioritizing-diseases-for-research-and-development-in-emergency-contexts, accessed on 21 June 2021). At present, medical countermeasures against CCHF remain controversial or experimental and the efficacy and safety of potential anti-CCHFV drugs also need comprehensive evaluation in standardized clinical trials. As a BSL-4 pathogen, CCHFV is strictly restricted to the special containment facilities for experimental manipulations of infections; moreover, suitable animal models also need to be further developed and optimized. Currently, they hamper virological studies and the assessments of prophylactic and therapeutic measures.

The entry-competent virus-like particle (tecVLP) system and recombinant fluorescent reporter virus which can be performed in the BSL-2 laboratory have been used in the initial screening of antivirals against CCHFV [22]. The identification of small molecule compounds inhibiting viral RNA synthesis can be conducted firstly with in vitro screening systems that rely on the availability of recombinant L protein or OTU protease and thus do not require high biosafety measures either [8][41]. In addition, computational virtual screening procedures provide both an alternative and a supplement to tiresome high-throughput screening, giving researchers the opportunity to hasten, facilitate and innovate the effectiveness of the overall drug discovery process. The resolved structures of several critical CCHFV proteins, including NP, the OTU domain of L, and glycoprotein (GP38), have and will continue to facilitate viral protein-targeting drug discovery based on structure and computational approaches [42][43][44][45].

In order to advance anti-CCHFV therapy development, animal models of CCHFV infection that can exhibit clinical signs similar to human disease are necessary in pre-clinical studies. Apart from the immunocompromised rodents, a lethal humanized mouse model transplanted with human hematopoietic CD34+ stem cells [46] and an immunocompetent mouse model which developed disease following infection with a mouse-adapted variant of CCHFV have been reported [47]. Better understanding of virology and virus–host interactions in the future may provide new clues for development of engineered animal models with specific virus-infection-associated host factor humanized, which are supposed to have significant advantages compared to those with common immune signaling proteins simply deleted. While current anti-CCHFV therapies have been assessed with limited animal models and clinical trials, future directions should focus on developing more appropriate animal models of CCHFV for the pre-clinical study of therapeutics.

Given the time-consuming nature of antiviral drug development and approval, repurposing the use of existing drugs in other conditions could be a strategy. A notable challenge for the development of antiviral drugs is the virus mutation, especially for CCHFV, which is an RNA virus with a high mutation rate. Some vital viral proteins involved in viral infection, such as the catalytic domain of RNA polymerases, can also be considered as promising targets for the development of pan-virus or pan-genus antivirals. In the case of CCHFV, the antivirals tested are mostly targeting RdRp and OTU protease, which themselves are notable targets for drug design; the discovery and development of inhibitors to other essential and conserved viral components in the CCHFV life cycle also need to be considered.

In view of many obstacles to progress, CCHF will clearly remain a significant public health threat for the foreseeable future. Further advances in areas such as structure analysis of viral proteins, immunocompetent animal model development, and the study of virus–host interaction would pave the way for effective medical countermeasures against CCHF. Additionally, successful research into CCHF therapeutics should also rely on collaboration among endemic countries.

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