Middle East respiratory syndrome coronavirus (MERS-CoV): challenges in identifying its source and controlling its spread

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Received 9 June 2013; accepted 10 June 2013

Abstract

Middle East respiratory syndrome coronavirus (MERS-CoV), a novel human coronavirus that caused outbreaks of a SARS-like illness in the Middle East, is now considered a threat to global public health. This review discusses the challenges in identifying the source of this fatal virus and developing effective and safe anti-MERS-CoV vaccines and therapeutics in order to control its spread and to combat any future pandemic.

Keywords: Coronavirus; MERS-CoV; SARS-CoV; Source; Vaccine; Therapeutics

1. Introduction

On 20 September 2012, Dr. Ali Moh Zaki, a virologist at Dr. Fakeeh Hospital, Jeddah, Saudi Arabia, first reported on the Program for Monitoring Emerging Diseases (ProMED-mail) that a novel coronavirus (nCoV) had been isolated from the lungs of a 60-year-old male patient with acute pneumonia and acute renal failure [1]. On 23 September 2012, the World Health Organization (WHO) was informed by the United Kingdom (UK) of a 49-year-old male Qatari national who had a travel history to Saudi Arabia and Qatar and showed symptoms of nCoV infection [2]. In November 2012, the virus was identified as a novel betacoronavirus, the closest relative of the bat coronaviruses HKU4 and HKU5, by Dr. Ron Fouchier’s group at the Erasmus Medical Center in Rotterdam, the Netherlands, and thus termed “hCoV-EMC” [3]. In May 2013, this virus was renamed as the Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV) by the Coronavirus Study Group of the International Committee on Taxonomy of Viruses [4], and the term was then adopted by WHO [5].

By 7 June 2013, WHO had been informed of 55 confirmed cases, including 31 deaths (a case fatality rate of 56%), from four countries in the Middle East (Saudi Arabia, Jordan, Qatar, and the United Arab Emirates), three countries in Europe (France, Italy, and the United Kingdom), and one country in Africa (Tunisia) (Table 1) [5]. Some of the patients reported in Europe were originally infected during their travel in the Middle East and became ill after their return to Europe, while others who had not been to the Middle East, but had been in close contact with laboratory-confirmed or probable cases, became infected because of limited person-to-person transmission. So far, eight MERS-CoV clusters have been reported. The largest cluster was linked to one healthcare facility in Al-Ahsa, Saudi Arabia, consisting of 25 patients and including 14 deaths. Two of these patients are healthcare providers who were infected after caring for patients with MERS-CoV infection [5,6]. This evidence strongly suggests human-to-human transmission involving different modes, such as droplet and contact transmission, although the efficiency of
Table 1

The cumulative number of MERS cases and deaths as of 6 June 2013 [5].

<table>
<thead>
<tr>
<th>Countries</th>
<th>Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middle East</td>
<td>45</td>
<td>28</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td>Jordan</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Qatar</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>United Arab Emirates (UAE)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Europe</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>United Kingdom (UK)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>France</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Italy</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Africa</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Tunisia</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>31</td>
</tr>
</tbody>
</table>

human-to-human transmission of MERS-CoV is lower than severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV) [6]. However, MERS-CoV may gain increased human-to-human transmissibility after its further adaptation and evolution in humans or as-yet unknown intermediate hosts, eventually causing a global pandemic like the one caused by SARS-CoV in 2003 [7–10].

On 27 May 2013 at the Sixtieth World Health Assembly, Geneva, Switzerland, Dr. Margaret Chan, the Director-General of WHO, pointed out that “the novel coronavirus is a threat to the entire world” because we still do not know where the virus hides in nature or how people become infected [11].

On 5 June 2013, the Obama administration designated MERS-CoV a threat to public health and national security and gave officials the authority to fast-track the approval of tests and treatments for MERS-CoV [12]. Dr. Kathleen Sebelius, the Secretary of the Department of Health and Human Services of the United States, made the designation, allowing the U.S. Food and Drug Administration (FDA) to quickly approve products after accepting an “emergency use application (EUA)” [13].

In mid-October of this year, more than two million Muslims will undertake the Hajj, an annual pilgrimage to Mecca, and they will remain in a confined geographical area over a five-day period. Medical authorities in Saudi Arabia have taken immediate steps to implement control measures over fears of a potential MERS-CoV pandemic resulting from this event, including the advisement to wear face masks in overcrowded areas [14].

Therefore, while researchers need to take appropriate steps now to identify the source of MERS-CoV, track down its intermediate host(s), and develop strategies for controlling its spread, these goals also bring a number of challenges.

2. Challenge in identifying the source of MERS-CoV

The first challenge confronting researchers is identifying the source of MERS-CoV. Genetically, we know that this virus is closely related to *Tylonycteris* bat CoV HKU4 (Ty-BatCoV HKU4) and *Pipistrellus* bat CoV HKU5 (Pi-BatCoV HKU5) in bats from Hong Kong. However, the molecular clock analysis suggests that these bat viruses are unlikely the direct ancestor of MERS-CoV [15].

MERS-CoV uses the evolutionarily conserved dipeptidyl peptidase 4 (DPP4) as its functional receptor [16], enters into the target cell via plasma or endosomal membrane fusion, and replicates in the host cell in a similar way as SARS-CoV does [17] (Fig. 1). It can infect various mammalian cell lines, such as primate, porcine, bat and rabbit cells [18], suggesting that MERS-CoV may have broad species tropism. It was reported that some MERS-CoV cases, as noted above, had a history of contact with animals, such as camels and goats [19], suggesting that MERS-CoV may have jumped from bats to these animals before infecting humans. However, its animal reservoir and intermediate hosts still have not been identified, which has significantly hindered the development of strategies to control this emerging infectious disease and combat the potential pandemic of MERS.

3. Challenge in designing MERS vaccines

To control MERS, we must develop an effective and safe vaccine, which constitutes a second challenge to researchers. However, the problems encountered in the development of SARS vaccines should be revisited before the MERS vaccines are designed. Some of the inactivated virus-based, DNA-based and viral vector-based vaccine candidates could induce Th2-mediated immunopathology or immunoenhancing pathology [20–24], raising concerns about the safety of the SARS vaccines.

Our previous studies have shown that the SARS vaccine candidates based on the receptor-binding domain (RBD) in the S1 subunit of the SARS-CoV spike protein is more effective and safer than the above-mentioned vaccine candidates [17,25,26]. By comparing the sequences of spike proteins of SARS-CoV and MERS-CoV, we predicted that a 286-amino acid fragment (residues 377–662) in the S1 subunit of MERS-CoV contains its RBD [27]. We strongly believe that the RBD in the MERS-CoV spike protein is therefore an important target for developing MERS vaccines.

Most recently, Chan et al. reported that the sera of some convalescent SARS patients contained antibodies that could cross-react or cross-neutralize MERS-CoV [28]. This raises a hope that people with histories of SARS-CoV infection might not be susceptible to MERS-CoV infection. However, our study demonstrated that the epitopes eliciting the cross-reactive antibodies may not be located in the RBD of SARS-CoV S protein [29]. Thus, it is doubtful whether these antibodies really have a role in cross-protection against MERS-CoV.

4. Challenge in developing anti-MERS therapy

To date, no effective antiviral therapeutics against MERS-CoV have been discovered. Clinical management is mainly supportive, placing emphasis on organ support for respiratory and renal failure. In cases of acute respiratory failure, the use of extracorporeal membrane oxygenation (ECMO) is expected to improve survival rates significantly [30].

Several nonspecific antiviral drugs, such as ribavirin, lopivavir, and type I IFN, have been used for treating SARS, but their limitations have been well documented [31,32].
although their actual efficacy in these patients is still unclear [31,32]. IFN-α was shown to inhibit in vitro MERS-CoV replication in cells [33], but it is unknown whether it works in vivo.

It has been thought that cytokine storm, a potentially fatal immune reaction characterized by the massive release of proinflammatory cytokines, is responsible for the deaths of patients infected by highly pathogenic avian influenza A (H5N1) virus or SARS-CoV [34,35]. Therefore, immunosuppressant or immunomodulatory drugs, which diminish inflammation during infection, are expected to have therapeutic benefit [36]. However, whether or not the immunosuppressant drugs should be used for treating MERS patients is debatable. First, no report has yet shown that cytokine storms are indeed responsible for the deaths of MERS patients. Second, cell host response to infection with MERS-CoV is much different from that to SARS-CoV infection [37]. Yuen and colleagues believed that corticosteroid should not be considered for treating MERS, particularly since patients with severe pneumonia and respiratory failure could be supported by ECMO until the cytokine storm is over [38].

Similar to HIV and SARS-CoV, MERS-CoV enters the target cells through its S2 protein-mediated membrane fusion (Fig. 1). Therefore, the S2 subunit of the MERS-CoV S protein may serve as a target for developing MERS-CoV fusion inhibitors. In the early 1990s, Jiang et al. [39] and Wild et al. [40] found that the peptides SJ-2176 and T20 derived from the HIV-1 gp41 HR2 domain had potent anti-HIV-1 activity. In 2003, T20 was approved by the U.S. FDA for treatment of HIV-infected patients who fail to respond to the current antiretroviral drugs [41,42]. In 2004, Jiang and colleagues identified an anti-SARS-CoV peptide (CP-1) from the SARS-CoV S protein S2 subunit of the HR2 domain [43]. Similar approaches could also be used to identify anti-MERS-CoV peptides. Different from the T20-based HIV/AIDS treatment regimen, which needs long-term injection [44], the MERS-CoV fusion inhibitor-based therapy would only require a regimen of a few days at the onset of MERS-CoV infection to save patients’ lives.

5. Conclusion

In conclusion, MERS-CoV, which originally caused outbreaks of a SARS-like illness in the Middle East, is now considered a threat to global public health. While its human-to-human transmission is so far limited, serious concerns over its pandemic potential have been raised. Therefore, researchers must take immediate steps to identify the source of this fatal virus and develop effective and safe anti-MERS-CoV vaccines and therapeutics in order to control its spread and to combat any future pandemic.

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Please cite this article in press as: L. Lu, et al., Middle East respiratory syndrome coronavirus (MERS-CoV): challenges in identifying its source and controlling its spread, Microbes and Infection (2013), http://dx.doi.org/10.1016/j.micinf.2013.06.003