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Therapeutic Considerations for Middle East Respiratory Syndrome Coronavirus

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Abstract

Middle East Respiratory Syndrome (MERS) is a severe respiratory illness first reported in Saudi Arabia that is caused by a coronavirus called MERS-CoV. This virus causes substantial fever, cough, and shortness of breath, and approximately half of the people afflicted have died. The MERS-CoV cases have occurred in or near the Arabian Peninsula, and to date no cases have been identified in the U.S. It is believed MERS-CoV is transmitted from ill people via contact and/or droplet; however, the virus has shown restricted transmission in communities. Recently, dipeptidyl peptidase-4 (DPP4) has been identified as a receptor for MERS-CoV. DPP4 is highly conserved across species and expressed by human bronchial epithelia, thus development of DPP4 inhibitors and those that target the virus-host interface may provide therapeutic opportunities to control MERS-CoV infection and disease.

Keywords: MERS; Coronavirus; MERS-CoV; Antiviral; Therapeutic; DPP4; CD26

Introduction

The emergence of novel infectious diseases continually poses a threat to animal and human health. This has been exemplified by the emergence of several viruses including pandemic H1N1 influenza virus, H7N9 influenza virus, H5N1 highly pathogenic avian influenza virus, and SARS-coronavirus (SARS-CoV). Recently, a novel respiratory virus has emerged from the Middle East, specifically Middle East Respiratory Syndrome (MERS) coronavirus (MERS-CoV) in June 2012 in Saudi Arabia [1]. MERS-CoV was first isolated from a 60 year old Saudi male who died of severe pneumonia [2]. Subsequently, other confirmed cases have been reported [3,4]. Coronaviruses are a family of viruses that cause a spectrum of illnesses in humans ranging from the common cold to severe acute respiratory syndrome [5]. Coronaviruses are also cause disease in a wide variety of animal species [5]. Perhaps the biggest unknown concerning the emergence of this disease is why MERS-CoV out breaks has been limited to the Middle East, and what the method of zoonotic transmission to humans.

MERS-CoV virus is thought to be an animal virus that resulted in human infections; however, there is currently no direct evidence for an animal origin. The fact that human cases have been sporadic with epidemiology suggesting that there has been long periods of time between cases and that the cases have occurred over wide-spread geographical areas has confounded identification of potential animal sources. It is important to note that MERS-CoV cases have occurred in clusters and in general without sustained human-to-human transmission [6,7], but human-to-human transmission has occurred in hospital settings, among family members, and at the work place [3,7,8]. Many questions remain unanswered as to the virus reservoir, and unlike SARS-CoV, bats do not seem to be the reservoir, and it remains unclear how people are becoming infected [4,9]. However, anecdotal exposure histories suggested that perhaps had been in contact with dromedary camels or goats, thus painting these animals as potential targets. Recent serological studies indicate that MERS-CoV or a related virus has infected camel populations, and rates of seroprevalence in sera from different locations suggest widespread infection [10,11].

Although the majority of coronavirus infections in humans are mild, the 2002 SARS-CoV outbreak and the emergence of MERS-CoV highlight the need to rapidly develop new disease intervention strategies [12,13]. Much had been learned from studies investigating the molecular biology of how coronaviruses co-opt the host for replication. Understanding the universal mechanisms used by all coronaviruses to replicate can be used in the development of therapeutics for coronavirus infections. One example is the finding that coronavirus replication and transcription are governed by a complex that is anchored in internal host cell membranes [14-16]. These membranes provide a framework for viral genome replication by localizing and concentrating host factors needed for replication. Thus, therapeutics that disrupts membrane anchoring may provide a path forward for governing virus replication and disease pathogenesis.

The novel human coronavirus discovered in 2012, initially termed human coronavirus-Erasmus Medical Center (hCoV-EMC) [17], but renamed MERS-CoV, was shown to replicate in several mammalian cell lines that express dipeptidyl peptidase 4 (DPP4) - also known as CD26 [18,19]. It was shown that DPP4 specifically co-purified with the receptor-binding S1 domain of the hCoV-EMC spike protein from lysates of susceptible Huh-7 cells [19]. Importantly, antibodies specific to DPP4 inhibited hCoV-EMC infection of primary human bronchial epithelial cells and Huh-7 cells, suggesting a strategy for therapeutic intervention and vaccination. DPP4 is a widely distributed protein that comes in secreted and membrane-bound forms, and is an evolutionary conserved serine-protease [20]. As serine-protease inhibitors to DPP4 are available [21], and serine-protease inhibitors are effective for several viruses [22-27], this is another path forward for potential antiviral treatments against MERS-CoV that need to be explored. In addition, such studies will contribute to our understanding of the pathogenesis of this emerging human coronavirus, and hopefully facilitate the development of intervention strategies.

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