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Review Paper:

The Pathogenicity of MERS-CoV, SARS-CoV and SARS-CoV-2: A Comparative Overview

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Abstract

The ongoing detrimental consequences of SARS-CoV-2 or COVID-19 are attributable to its remarkable pathogenesis and modes of transmission. Originating from a common ancestor of the previous coronavirus outbreaks, MERS-CoV and SARS-CoV-1, the former has been evolved in terms of its pathogenic mechanisms, routes of transmission and the extent of infection. The comprehensive evaluation of these modifications at the molecular level would reveal astonishing details about the extensive lethality of the current SARS-CoV-2 outbreak.

Further, these details can be utilized for the development of effective and specific treatment methods. This review elaborates the comparative assessment of the viral characteristics of coronaviruses: MERS-CoV, SARS-CoV-1 and SARS-CoV-2. With the comparative account, the study endeavours to leave a clear picture explaining the reason behind the extensive lethality of the current SARS-CoV-2 pandemic.

Keywords: SARS-CoV, MERS-CoV, Pathogenesis, Transmission, Infection.

Introduction

The past two decades of the 21st century have witnessed several malicious biological hazards that took the entire globe into an appalling situation including Ebola, Zika and Nipah viral outbreaks to name a few. However, they stood no match for the disastrous outbreak of severe acute respiratory syndrome-2 (SARS-CoV-2) or COVID-19 and its consequences.³⁴ Since its emergence in December 2019, the latter has resulted in a steep escalation in mortality rates. Expanding to the different parts of the world, it gained a status of the pandemic within no time due to its profound pathogenicity, transmission and resistance to the available therapeutic options.^{54,65}

Though there were reports of outbreaks of other viruses from the same family, they were not as infectious as of the SARS-CoV-2. For example, four endemic human coronaviruses HCoV-229E, -NL63, -HKU1 and -OC43 were known to circulate in human blood yet causing no major casualties. It was reported that HCoV-229E and -OC43 accounted for 15–

29% of respiratory pathogens with relatively reduced viral load which serves as a rough approximation.^{15,76} The other two viruses HCoV-NL63 and -HKU1 were discovered only in 2004 and 2005 respectively, leaving negligible chances of a major outbreak due to their endemic nature.¹⁵ But the health crisis began in 2003 when China reported the first of their epidemic kind, the SARS-CoV-1 or severe acute respiratory syndrome-1. This epidemic was responsible for the death of 919 people and 8422 cases, with the fatality rate of 11.0%.⁷⁶

The zoonotic transmission of SARS-CoV-1 from December 2003 to January 2004 became a pavement for researches into the origin of this epidemic. Though it was declared as over in 2004 with no further cases detected, demonstration of SARS-CoV-like viruses found in bats revealed the chance of re-emergence of SARS in future.⁴⁴

In support of this prediction, another epidemic coronavirus known as MERS-CoV (Middle East Respiratory Syndrome Coronavirus) was detected in the sputum of a deceased pneumonia male patient with renal failure in Saudi Arabia. The epidemic caused 858 deaths and 2494 cases with a fatality rate of 34.4% from 27 different countries.⁷⁶ The increased fatality rate was attributed to nosocomial infections and international travels that made it a global threat. In May 2015, South Korea reported the outbreak of MERS-CoV due to a returned individual from Middle East.¹⁹ Besides a tremendous progression is made towards deciphering the biological features of SARS-CoV-1 and MERS-CoV at an unprecedented speed, a shocking and detrimental outbreak of COVID-19 has resulted in 387,155 deaths and 6,535,354 confirmed cases from 213 countries across the globe with an increasing death rate as of 6th June 2020.⁷¹

Although MERS-CoV and SARS-CoV-1 share several common and important features that are responsible for nosocomial transmission, preferential viral replication and viral immunopathology, SARS-CoV-2 stands with few uncommon characteristics that make it more malicious.⁵⁷ Though it has been isolated and the mechanisms of its pathogenicity and infectivity are deciphered, there is much room to know and highlight the viral mode of action, life cycle and pathogenicity.¹⁷ This review focuses on the effective life cycle, severity, transmission modes, therapeutic options of SARS-CoV-2 to highlight its pathogenicity over the other two epidemic coronaviruses.

Animal Origin and Evolution

It becomes essential to note that two of the three viral outbreaks emerged from China and all the three shared the same zoonotic origin. China is said to be a homeland for diverse climates which bring about greater biodiversity. This allows bats and bat-borne viruses, most of them are ICTV coronavirus species, to grow in it making the country a hotspot for the viral growth. On the other hand, animals and meat products are extensively sold in Chinese wet markets which might have caused these viral outbreaks.²⁰

Coronaviruses belong to the subfamily *Coronavirinae* in the family *Coronaviridae* and the order *Nidovirales*. The subfamily comprises four genera – α , β , γ and δ , based on their genomic constituents and phylogenetic relationships. α and β genera notably affect the mammals including humans whereas the other two affect birds. SARS-CoV and MERS-CoV are said to be highly pathogenic among the coronaviruses and can cause a severe acute respiratory syndrome in humans while the other 4 endemic viruses including HCoV-229E, -NL63, -OC43 and -HKU1 can only result in the development of mild upper respiratory disorders.

The origin of the SARS-CoV, MERS-CoV, HCoV-229E and -NL63 is expected to from bats whereas HKU1 and HCoV-OC43 are likely originated from rodents. Several studies conducted showed that bats are the origin of coronaviruses. But few of the clear examinations conducted at the molecular level revealed that the SARS-CoV-1 was found to be originated from both bats as well as palm civets.

Genome analysis of bats and palm civets revealed that a 29-nt sequence acts as a marker which is also expressed in humans as well⁵⁸ indicating the route of transmission of the virus to humans. However, a probe-based next-generation sequencing (NGS) showed that SARS-CoV-1 seems to have originated only from bats,⁴¹ strongly supporting the idea of SARS originating from bats. Analysis of recombination has showed that civet SARS-CoV strain SZ3 was produced due to the recombination of WIV16 and Rf4092, the 2 existing bat strains revealing the role of palm civet as a reservoir as well as an intermediate host.¹⁷

Also, the presence of accessory proteins and other several gene products showed 89-90% genome similarity between bats and humans whereas phylogenetic evaluation proved the same.⁵⁸ In addition to palm civets, SARS-CoV-1 was also reported to be found in raccoon dogs of Chinese origin. The spike protein sequence SZ13 of raccoon dogs was found to be identical to SZ16 of palm civet.

Similarly, 2 other proteins, A030G and A031G are found to be identical to A022G indicating that raccoon dogs are also the potential reservoirs and intermediate hosts of SARS-CoV-1.⁷⁴ These studies insisted on the role of bats as primary hosts and other animals as intermediates. Apart from palm civets, bats were also found to be the potential reservoirs of

MERS-CoV as well. A study found that 12 of the bat cells were susceptible to MERS-CoV infection based on which it was reported that the virus can replicate in the cells. The mRNA sequence analysis also revealed the presence of DPP4 or CD26, a receptor which is used by the MERS-CoV to enter the host cell.³⁸ Apart from bats, MERS-CoV is also reported to be originated from dromedary camels. Identification of prevalent MERS-CoV specific antibodies present in camels from the Middle East, Africa, Asia and detection of infections in camel serum showed the presence of virus from 30 years.

Genomic sequence of *Tylosycteris* bat HCoV-HKU4, *Pipistrellus* bat HCoV-HKU5 and MERS-CoV revealed that they are phylogenetically related.¹⁷ Further, the respiratory sample analysis of patients, as well as camels affected with MERS-CoV revealed the presence of nearly identical genomes⁵² indicating the role of dromedary camels as a potential reservoir and an intermediate host, though the original infection is said to be caused by bats.

In the vista, a coronavirus isolated from Malayan pangolin showed a 99% similarity with SARS-CoV-2, although it showed 96% similarity in case of bats. Five of the six amino acids from the receptor-binding domains (RBD) of both pangolin-CoV and SARS-CoV-2 are found to be the same. In support, the infected pangolins exhibited pathological symptoms like humans suffering from COVID-19 suggesting that they were a potent intermediate host between bat and humans. Studies on the S, N and ORF1a/1b genes suggested that SARS-CoV-2 was transmitted to humans by adapting evolutionary mechanisms. However, a comparative analysis of genetic data showed that SARS-CoV-2 originated from the recombination of pangolin-CoV and bat-CoV-RaTG13 virus,⁴⁸ yet again supporting the role of pangolin as a reservoir. But a contradictory theory suggests that laboratory manipulation of SARS-CoV-1 and MERS-CoV resulted in the genesis of SARS-CoV-2.⁴¹

In addition, another study suggests the involvement of snake coronavirus in the production of recombinant SARS-CoV-2 alongside bat coronavirus. But the truth is yet to be revealed about these suggestions.³⁶ Though the MERS-CoV and SARS-CoV-1 had a definite primary host (bat) and several confirmed and potential intermediate hosts, SARS-CoV-2 was not found to be related with a definite host. The evolutionary mechanisms possessed by SARS-CoV-2 resulted in its effective transmission over the others. Hence, further studies are essential to confirm the role of intermediate hosts and to examine the manipulation of genetic recombination to control the outbreak of such a pandemic in future.⁷³

Structural and Genomic Features

All the three epidemic coronaviruses share common features in terms of their structures and life cycles. Though one can notice few minute variations in case of their genomes, they ultimately lead to differences in the extension of