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Mini Review

Coronavirus (CoV) Pathogenesis and Host Immunology

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Received: June 26, 2020; **Published:** September 10, 2020

Abstract

Current COVID-19 pandemic by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is foremost global public health issue. The relationship of this deadly virus with the previous Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 and with the acute respiratory syndrome coronavirus (SARS-CoV) in 2002 is being studied in several aspects including the evolution, transmission, genetics, epidemiology, pathogenesis and host immune response; and about the treatment strategies comprising the candidate drugs and possible vaccines. Current review briefly summarized the pathogenesis scheme of all the β-coronaviruses along with the host immune response.

Keywords: *COVID-19 Pandemic; SARS-CoV-2, SARS-CoV; MERS-CoV; Pathogenesis; Host Immune Response*

Introduction

Among the 4 genera of coronaviruses (CoV); i.e. alpha (α), beta (β), gamma (γ), and delta (δ), the β-CoVs comprises the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) possessing highly conserved genomic organization scheme [1-4]. Both SARS-CoV and MERS-CoV have been reported to originate from bats; and then SARS-CoVs were transmitted to humans from market civets; while the MERS-CoVs from the dromedary camels; and SARS-CoV-2, which also originated from bats, pangolins, and snakes, were further spilled over to the humans whose transmission was afterwards facilitated by human-to-human close contact (via sneezing and coughing) [1,3]. The severe clinical onset by SARS-CoV- 2 infection has been noticed as development of the acute respiratory distress syndrome (ARDS) that has been also found in case of SARS-CoV and MERS-CoV infections [3]. SARS-CoV-2 has appeared to be the most dynamic pandemic causing 479133 deaths out of 9296202 infected cases so far [5]. Current review shortly summarized the pathogenic scheme of SARS-CoV-2 in relation to the previous coronavirus strains.

Pathogenesis spectra between SARS-CoV-2, SARS-CoV and MERS-CoV

The spike (S) protein, both from the SARS-CoV-2 and SARS-CoV bind to the angiotensin-converting enzyme 2 (ACE 2) receptor of the host whereas MERS-CoV utilizes the host receptor Dipeptidyl peptidase 4 (DPP4); however, SARS-CoV-2 possess a longer spike protein than that of SARS-CoV [2]. The SARS-CoV-2 entry may depend on the non-neutralizing antibodies while in case of SARS-CoV [2,4,6], the neutralizing antibodies can hinder the viral entry; and in case of the MERS-CoV entry mainly relies on the host natural killer (NK) cell inactivation [2]. The pathogenesis of SARS-CoV-2 and SARS-CoV have been observed to be highly linked to the elevation of the pro-inflammatory cytokine and chemokine levels (i.e. the cytokine storm) whereas MERS-CoV pathogenesis was linked with the interferon

(IFN) antagonism [2]. Upon the ACE receptor engagement with the S protein, the cellular surface serine protease TMPRSS2 (the plasma membrane-associated type II transmembrane serine protease) is engaged to trigger the spike protein (S) to accelerate the membrane fusion that is needed for the release of the viral genome into the host cell cytosol [3]. In addition, the antibody-dependent enhancement (ADE) of viral entry may occur whereby a neutralizing monoclonal antibody (Mab, through the IgG Fc receptor) targets the receptor binding domain (RBD) of the spike, and subsequently allows it to undergo certain conformational changes which allow the viral entry into the IgG Fc receptor-expressing cells [2,3,6].

Pathogenic events after the SARS-CoV-2 entry and host immunology

The pathophysiological impact in the CoV affected patients largely depends on the accumulation/elevation of the levels of pro-inflammatory cytokines and chemokines (generation of the cytokine storm) [7,8]. Upon the viral entry mediated by ACE2 and TMPRSS2, the active replication with the subsequent release of the virus instigate the host cell to undergo death and inflammation together with the release of damage-associated molecular patterns (DAMPs) including ATP, nucleic acids, etc [10]. The antibodies produced by the B cells may also accelerate the infection through the antibody-dependent enhancement (ADE) [7]. The DAMPs are recognized by the neighboring epithelial cells, endothelial cells and the alveolar macrophages, which then trigger the production of interleukin (IL)-6, macrophage inflammatory protein 1α (MIP1α), MIP1β and MCP1, which attract the monocytes, macrophages, T cells and IFNγ to the site of infection; leading to ARDS and sometimes to the multi-organ damage [2,3,5,7].

Pathogenesis mediated by SARS-CoV and immunological response

Immunological response upon viral infection can either limit virus spreading or surprisingly can cause the pathological damages to the host tissues which mainly depends on the accumulation of pro-inflammatory cytokines [1,2,8,9]. Upon the SARS-CoV infection, the macrophages, dendritic cells, and the alveolar epithelial cells trigger a significant increase in the pro-inflammatory chemokines including the macrophage inflammatory protein-1α (MIP-1α), IP-10 (similar to that in SARS-CoV-2), interleukin (IL) 2, 5, 6 and IL-8, monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor alpha (TNF-α) and certain chemokines [10].

Pathogenesis mediated by the MERS-CoV

Upon MERS-CoV entry into the host cell, the type I interferon (IFN)-mediated innate immune response is activated through the production of type I IFNs (IFN-α and IFN-β) [11,12]. MERS-CoV pathogenesis stringently relies on the ORF4a (dsRNA binding protein), which acts as an antagonist of the anti-viral activity of IFN as it blocks the IFN production, activation of NF-κB (the nuclear factor kappa-light-chain-enhancer of activated B cells); and hinders the IFN-stimulated response elements which promotes the IFN-induced JAK/STAT signaling pathway [12,13].

Therapeutic strategies against SARS-CoV-2

According to the *in silico* study, cell culture models, and the patient trials, so far several potential drugs have been identified to be effective against SARS-CoV-2 infection. Indeed, all the drugs are currently under trial; however, remdesivir, chloroquine/hydroxychloroquine, ribavirin, favipiravir, cepharanthine and opinavir/ritonavir have been well recognized to possess the potential anti-viral activities against the SARS-CoV [14]. This is to be mentioned that still there is no vaccine against the COVI-19 infections although several candidate vaccines are under trial.

Conclusion

Current review briefly summarized the pathogenic events of the b-coronaviruses in association to the host immunology. Further studies on the corresponding signal transduction mechanisms would augment the understanding of the pathogenic events which in turn would be helpful to design appropriate drugs and vaccines.

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Volume 16 Issue 10 October 2020