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REVIEW

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Overlapping and discrete aspects of the pathology and pathogenesis of the emerging human pathogenic coronaviruses SARS-CoV, MERS-CoV, and 2019-nCoV

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Abstract

First reported from Wuhan, The People's Republic of China, on 31 December 2019, the ongoing outbreak of a novel coronavirus (2019-nCoV) causes great global concerns. Based on the advice of the International Health Regulations Emergency Committee and the fact that to date 24 other countries also reported cases, the WHO Director-General declared that the outbreak of 2019-nCoV constitutes a Public Health Emergency of International Concern on 30 January 2020. Together with the other two highly pathogenic coronaviruses, the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), 2019-nCov and other yet to be identified coronaviruses pose a global threat to public health. In this mini-review, we provide a brief introduction to the pathology and pathogenesis of SARS-CoV and MERS-CoV and extrapolate this knowledge to the newly identified 2019-nCoV.

KEYWORDS
coronavirus, immnopathology, immune responses, pathogenesis, respiratory tract, virus classification

1 | INTRODUCTION

In late December 2019, clusters of patients with pneumonia of unknown etiology were reported by the local health facilities in Wuhan, Hubei Province, China.[1] In early January 2020, the causative agent of mysterious pneumonia has been identified as a novel coronavirus by several independent laboratories located in China. The causative virus has been temporarily named as 2019 novel coronavirus (2019-nCoV) by the World Health Organization.[2] According to the daily report of the World Health Organization, the epidemic of 2019-nCoV so far caused 45,171 laboratory confirmed cases and 1114 death in China, as well as 441 confirmed cases and 1 death in 24 other countries by 12th February 2020.

Coronaviruses are distributed broadly among humans and animals and cause respiratory, enteric, hepatic, and neurologic diseases. So far, 2019-nCoV is the seventh member of the family of coronaviruses that infects humans. Preceding the 2019-nCoV epidemic, the 21st century has already seen outbreaks caused by two other highly pathogenic coronaviruses, the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV). These outbreaks result from zoonotic coronavirus crossing the species barrier and causing high morbidity and mortality in human populations.[3,4] The 2019-nCoV, SARS-CoV, and MERS-CoV show several similarities regarding the clinical presentations, which can vary from asymptomatic infection to severe disease; severe acute respiratory syndrome.[5,6] Therefore, our current knowledge of the biology and pathology of SARS-CoV and MERS-CoV may provide clues for ongoing and future research efforts concerning the investigation of the 2019-nCoV. In this review, we try to apply our current understanding of the pathology and pathogenesis of SARS-CoV and MERS-CoV for the characterization of 2019-nCoV.

2 | PATHOLOGICAL CHANGES IN SARS-CoV INFECTION

The available pathology data for SARS-CoV infections were mainly obtained from autopsies. The predominant visceral macroscopic changes in fatal SARS-CoV cases have been edematous lungs with increased gross weights and multiple areas of congestion, enlargement of lymph nodes in the pulmonary hila and the abdominal cavity, as well as a diminished spleen size and reduced spleen weights.[7,8] Morphological changes were bronchial epithelial denudation, loss of cilia, and squamous metaplasia.[7] The histological feature in the early phase of pulmonary SARS-CoV infections is commonly associated with acute diffuse alveolar damage, while later phases of the disease demonstrate a combination of diffuse alveolar damage and acute fibrinous and organizing pneumonia.[9] Large numbers of SARS-CoV particles and genomic sequences were detected within circulating lymphocytes, monocytes, and lymphoid tissues, as well as in epithelial cells of the respiratory tract, the intestinal mucosa, the epithelium of renal distal tubules, neurons in the brain, and tissue-resident macrophages residing in different organs.[10] Co-localization of SARS-CoV RNA and cellular cytokeratins within the lung was evident by immunofluorescent in situ hybridization, suggesting that pneumocytes become infected.[11] Accordingly, electron microscopic examinations also showed SARS-CoV virions and nucleocapsid inclusions in pneumocytes.[12] Additionally, SARS-CoV may occasionally be identified in the alveolar macrophages of the lung.[12]

3 | PATHOGENESIS OF SARS-COV INFECTION

The mechanisms underlying more severe pathogenicity of SARS-CoV are so far not fully understood. Extensive lung damage in SARS-CoV-infected patients appears to be associated with high initial virus titers,[13] increased monocyte, macrophage, and neutrophil infiltration in the lungs,[7] and elevated levels of serum proinflammatory cytokines and chemokines.[14] Therefore, the clinical deterioration of SARS-CoV infection may result from a combination of direct virus-induced cytopathic effects and immunopathology induced by a hyper-cytokinemia or a "cytokine-storm." Studies of the changes in cytokine/chemokine profiles during SARS-CoV infection revealed increased levels of circulating cytokines, such as tumor necrosis factor α (TNF-α), CXCL-10, interleukin-6 (IL-6), and IL-8, likely contributed to the poor prognosis in SARS-CoV infections.[15]

High serum levels of proinflammatory cytokines (IL-1, IL-6, IL-12, Interferon γ [IFN-γ], and transforming growth factor-β) and chemokines (CCL2, CXCL9, CXCL10, and IL-8) were found in patients with SARS with severe disease compared to individuals with uncomplicated SARS.[14,16–18] In addition, the early induction of CXCL10 and IL-2, as well as the subsequent hyperproduction of IL-6 with a coinciding lack of IL-10 production are thought to contribute to the immuno-pathological processes involved in lung injury during SARS-CoV infection.[17] Additionally, robust and persistent expression of IFN-α, -γ and IFN-stimulated genes (ISGs) accompanied early SARS sequelae.[19] It has also been shown that SARS-CoV infections result in a delayed expression of type I IFN.[20] The delayed-type I IFN signaling, which was accompanied with robust virus replication, was found to promote the accumulation of pathogenic inflammatory monocyte/macrophages, resulting in elevated lung cytokine/chemokine levels, vascular leakage, and impaired virus-specific T cell responses.[21]

4 | PATHOLOGICAL CHANGES ASSOCIATED WITH MERS-CoV INFECTIONS

The understanding of pathophysiological changes caused by MERS-CoV infections relies on limited numbers of autopsy and biopsy cases. Few studies indicate that the pathological features of MERS-CoV infection include exudative diffuse alveolar damage with hyaline membranes, pulmonary edema, type II pneumocyte hyperplasia, interstitial pneumonia (which was predominantly lymphocytic), and multinucleate syncytial cells.[22,23] Bronchial submucosal gland necrosis was also observed.[22] These bronchial lesions comprise the pathologic basis for the respiratory failure and radiologic abnormalities of MERS-CoV infection.[24] Target cells of the MERS-CoV infection in the lung include pneumocytes, multinucleated epithelial cells, and bronchial submucosal gland cells.[22] All of these cells express a multifunctional cell surface protein, called *dipeptidyl peptidase 4* (DPP4; also known as CD26), constituting the primary entry receptor of MERS-CoV.[25] Ultrastructurally, viral particles were found in the pneumocytes, pulmonary macrophages, macrophages infiltrating the skeletal muscles, and renal proximal tubular epithelial cells.[23] Consistent with the ultrastructural findings in the kidney, renal biopsies demonstrated acute tubulointerstitial nephritis and acute tubular sclerosis with proteinaceous cast formation.[26]

5 | PATHOGENESIS OF MERS-CoV INFECTIONS

DPP4, the entry receptor of MERS-CoV, is widely expressed on epithelial cells in the kidney, alveoli, small intestine, liver, prostate, and on activated leukocytes,[27] suggesting that the range of MERS-CoV tissue tropism is broader than that of any other coronavirus.[28] Accordingly, MERS-CoV was found to be able to infect many human immune cells, including dendritic cells,[29] macrophages,[30] and T cells.[31] MERS-CoV infections of DCs and macrophages result in robust and sustained production of proinflammatory cytokines and chemokines, such as TNF-α, IL-6, CXCL-10, CCL-2, CCL-3, CCL-5, and IL-8.[29,30] Proinflammatory and immune-attracting capacities of these cytokines are thought to cause (or at least contribute to) immune cell infiltration into the lower respiratory tract of infected patients and the observed severe inflammation as well as tissue damage.[30] MERS-CoV infections of T cells results in apoptosis mediated by a combination of extrinsic and intrinsic apoptosis pathways.[31] Through this mechanism, MERS-CoV evades the T cell response in the

peripheral blood and lymphoid organs, which may contribute to virus spread and the severe immunopathology.[31] Moreover, it has been reported that MERS-CoV can also induce apoptosis of both kidney and lung cells through upregulation of Smad7 and fibroblast growth factor 2 (FGF2) expression.[32]

6 | 2019-nCoV

Approximately 1 month after the onset of the outbreak, several virological and clinical aspects of the 2019-nCoV and associated disease are still under investigation. However, the field is rapidly moving forward. Nevertheless, findings from several reports await independent confirmation and have to be regarded with precautions.

The genome of 2019-nCov was sequenced very early during the outbreak.[5] This enabled rapid development of point-of-care real-time reverse transcription-polymerase chain reaction diagnostic tests specific for 2019-nCoV.[33] The genetic sequence analysis revealed that the 2019-nCoV belongs to the β-coronavirus genus, with a 79.0% nucleotide identity to SARS-CoV and 51.8% identity to MERS-CoV.[34] Furthermore, it has been reported that nCoV-2019 is 96% identical across the entire genome to a bat coronavirus.[35] Inoculation of the 2019-nCoV onto surface layers of human airway epithelial cells in vitro causes cytopathic effects and cessation of the cilium beating of the cells.[5] The 2019-nCoV infection was of clustering onset that is more likely to affect older males with comorbidities and can result in severe and even fatal respiratory diseases.[36,37] The major clinical symptoms resulting from 2019-nCoV infection at the prodromal phase include fever, dry cough, myalgia, fatigue, and diarrhea.[38] Many patients also developed dyspnea and lymphopenia. Complications of 2019-nCoV infections included acute respiratory distress syndrome, RNAaemia, acute cardiac injury, and secondary (super-)infections.[38] All reported cases, including asymptomatic patients, had abnormal findings concerning the chest computed tomography (CT) as indicated by bilateral ground-glass opacity.[6,38] The prototypical findings of chest CT images of seriously ill patients requiring intensive care unit (ICU) admission were bilateral multiple lobular and subsegmental areas of consolidation.[38] Initial plasma IL-1β, IL-1Rα, IL-7, IL-8, IL-9, IL-10, basic FGF, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1A, MIP1B, PDGF, TNF-α, and vascular endothelial growth factor concentrations were higher in 2019-nCoV-infected patients as compared to healthy controls. Moreover, ICU patients showed higher plasma levels of IL-2, IL-7, IL-10, GSCF, IP10, MCP1, MIP1A, and TNF-α than non-ICU patients.[38] These results suggest that immunopathology may also play a relevant role in the development of disease severity.

7 | SUMMARY AND OUTLOOK

The comprehensive lessons learned from the SARS-CoV and MERS-CoV outbreaks provide, despite their inherent tragedy, valuable experiences and insights into how to fight the 2019-nCoV epidemic. Drugs which inhibit viral dissemination and disrupt viral replication may reduce the coronavirus-induced direct cytopathic effects, and treatments which restrain host inflammatory responses (eg, by antibodies or compounds neutralizing cytokines or their cognate receptors, such as anti-IL-6, anti-IL-6R, or anti-IL-1β), ideally in the respiratory tract only, may reduce virus-triggered immunopathologies. We infer that a combination of such treatments would be the most suitable therapeutic strategy for more severe human coronavirus infections. However, we must bear in mind that currently, no specific antiviral treatment is available for SARS, MERS, and 2019-nCoV, and therefore further research into the pathogenesis of human coronavirus infection is imperative for identifying appropriate therapeutic targets.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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