View Point

COVID-19, the novel coronavirus 2019: current updates and the future

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ABSTRACT

COVID-19 is a new strain that has not been previously identified in humans. It is large, enveloped, single-stranded RNA virus. The clinical features range from the common cold to more severe diseases i.e., MERS and SARS. Incubation period ranges between 1-12.5 days (median 5-6 days). As on 07 March, 2020 total confirmed cases are 1,01,927 with 3486 deaths in 93 countries/territories/areas. The various lab tests for COVID-19 virus are NAAT, serological testing, viral sequencing and viral culture. Many aspects of this virus is still not understood. The authors in this article describe studies to know the pathogenesis as well as immunological response with use of animal methods. Authors also discuss genetic engineering, evaluation of activation and inflammatory activity of myeloid cells during pathogenic human coronavirus, etc. that can help in prevention and treatment of COVID-19 in near future.

Keywords: Coronavirus, COVID-19, MERS-CoV, SARS-CoV

INTRODUCTION

A novel coronaviruses (nCoV) is a new strain that has not been previously identified in humans. Coronaviruses are large, enveloped, single-stranded positive-sense RNA viruses that cause both significant human and veterinary disease. Now named as COVID-19 (C-O-V-I-D hyphen one nine). Previously called novel coronavirus 2019 (nCoV-2019).[1] These viruses cause illness ranging from the common cold to more severe disease such as Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Distress Syndrome (SARS-CoV). In early December 2019 a patient was diagnosed with an unusual pneumonia in the city of Wuhan, China. By December 31 the World Health Organization (WHO) regional office in Beijing had received notification of a cluster of patients with pneumonia of unknown cause from the same city.1 Over the next few days, researchers at the Wuhan Institute of Virology performed metagenomics analysis using next-generation sequencing from a sample collected from a bronchi-alveolar lavage and identified a novel corona-virus as the potential aetiology. Prior to the severe acute respiratory syndrome-CoV (SARS-CoV) outbreak in 2003, human CoVs were only known to cause mild, self-limiting upper respiratory diseases. Approximately 10 years after the emergence of SARS-CoV in 2012, Middle East respiratory syndrome (MERS)-CoV emerged in the Middle East where it then spread to 27 different countries. As of 07 March, 2020, 1,01,927 cases of COVID-19 have been reported worldwide of which cases from China to be 80,813 that is 79.28%. The outbreak is linked to 3486 deaths (106 new). Currently the number of infections outside China are 21,110 confirmed cases that is 20.71% with cases have been detected in 93 countries/territories/areas with 413 death. Italy has reported a rapid increase in cases of laboratory-confirmed coronavirus (COVID-19) since 21 February 2020. Viewing point towards India which has 31 confirmed cases of COVID-19.

It appears that compared with the other 2 zoonotic coronaviruses that occurred in the last 20 years (severe

acute respiratory syndrome [SARS] in 2002 and Middle East respiratory syndrome [MERS] in 2012), 2019-nCoV seems to have greater infectivity (higher Ro) and lower case fatality rate.[2]

From genetic sequencing data, it appears that there was a single introduction into humans followed by human-to-human spread. This novel virus shares 79.5% of genetic sequence with SARS-CoV and has 96.2% homology to a bat corona virus.[2] In addition, COVID - 19 shares the same cell entry receptor with virus.

What is yet unclear is which animal is the intermediate species between bats and humans? For SARS it was civet cats, for MERS it is camels. While the source of 2019-CoV is yet unknown, early on the Huanan Seafood Wholesale Market was linked epidemiologically.[2,3]

The incubation period of this virus has been reported to be 5-6 days, although there is suggestion that it may be as long as 14 days. It is unclear when transmission begins. Cases reported stated that transmission during asymptomatic phase, it is likely that majority of secondary cases come from symptomatic individuals.

The clinical syndrome is nonspecific and characterised by fever and dry cough in the majority of patients, with about a third experiencing shortness of breath. Some patients have other symptoms such as myalgias, headache, sore throat and diarrhoea.[4] The median age of patients is between 49 and 56 years.[4,5] It is rarely noticed in children.

Although most cases appear to be mild, all patients admitted to the hospital have pneumonia with infiltrates on chest x-ray and ground glass opacities on just computed tomography.[5,6] About a third of patients subsequently develop Acute Respiratory Distress Syndrome and require care in critical care unit. This is particularly true for patients with comorbid conditions such as diabetes or hypertension. When a patient presents with fever and respiratory symptoms (in particular a dry cough), clinicians should obtain a detailed travel history. In the event of a person under investigation, clinicians should immediately notify their health care infection prevention team, as well as their local or state health department.

Clinicians should test for other respiratory pathogens and should consider prescribing OSELTAMIVIR pending results of influenza testing. Health care practitioners should wear N95 respirators. To date, the management of infection has been largely supportive. LOPINAVIR/RITONAVIR is being investigated (Chinese clinical trial registry identifier: ChiCTR2000029308) based on previous studies suggesting possible clinical benefits in SARS and MERS.[1] In addition, REMDESIVIR, available through compassionate use, has also been tried and this latter anti-viral was used in first US patient identified.

WHO on 30 January 2020 declared the outbreak a public health emergency of International concern. What interventions will ultimately control this outbreak is unclear because there is currently no vaccine, and the effectiveness of antivirals is unproven. However basic public health measures such as staying at home when ill, hand washing, and respiratory etiquette including covering the mouth and the nose during sneezing and coughing were effective in controlling SARS. Clinicians and public health authorities, must work together to educate the public by providing accurate and up-to-date information and by taking care of patients with respiratory illness in a timely and effective way.

Criteria to guide evaluation of patient under investigation for 2019 novel coronavirus

Based on clinical features and epidemiological risk:

- Fever or signs or symptoms of lower respiratory illness like cough and or shortness of breath with any person, including healthcare workers, who has had contact with a laboratory confirmed coronavirus patient within 14 days of symptoms onset.
- Fever and signs or symptoms of lower respiratory illness like cough and or shortness of breath with history of travel from Hubei Province, China, within 14 days of symptoms onset.
- Fever and signs or symptoms of lower respiratory illness like cough and or shortness of breath requiring hospitalisation with history of travel from mainland China within 14 days of symptoms onset.

If a patient under investigation is confirmed, clinician should notify their health care prevention team as well as local or state health department.

Situation in numbers (as on 07 March 2020)

Total and new cases in last 24 hours

- Globally : 1,01927 confirmed (3735 new)
- China : 80,813confirmed (102 new); 3073deaths (28 new)
- Outside of China : 21,110confirmed (3633new)
- 93 countries/territories/areas
- Deaths outside China: 413(78 new)
- 3486 death (106 new)

WHO risk assessment

- China : Very High
- Regional Level : Very High
- Global Level : Very High

China has revised their guidance on case classification for COVID-19, removing the classification of "clinically diagnosed" previously used for Hubei province, and retaining only "suspected" and "confirmed" for all areas,

the latter requiring laboratory confirmation. Some previously reported "clinically diagnosed" cases are thus expected to be discarded over the coming days as laboratory testing is conducted and some are found to be COVID-19-negative.

Strategic objectives

WHO's strategic objectives for this response are to:

- Limit human-to-human transmission including reducing secondary infections among close contacts and health care workers, preventing transmission amplification events, and preventing further international spread from China;
- Identify, isolate and care for patients early, including providing optimised care for infected patients;
- Identify and reduce transmission from the animal source;
- Address crucial unknowns regarding clinical severity, extent of transmission and infection, treatment options, and accelerate the development of diagnostics, therapeutics and vaccines;
- Communicate critical risk and event information to all communities and counter misinformation;
- Minimise social and economic impact through multisectoral partnerships.

This can be achieved through a combination of public health measures, such as rapid identification, diagnosis and management of the cases, identification and follow up of the contacts, infection prevention and control in health care settings, implementation of health measures for travellers, awareness-raising in the population and risk communication.

Recommendations and advice for the public

During previous outbreaks due to other coronavirus (Middle-East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS), human-to-human transmission occurred through droplets, contact and fomites, suggesting that the transmission mode of the COVID-19 can be similar. The basic principles to reduce the general risk of transmission of acute respiratory infections include the following:

- Avoiding close contact with people suffering from acute respiratory infections.
- Frequent hand-washing, especially after direct contact with ill people or their environment.
- Avoiding unprotected contact with farm or wild animals.
- People with symptoms of acute respiratory infection should practice cough etiquette (maintain distance, cover coughs and sneezes with disposable tissues or clothing, and wash hands).

- Within health care facilities, enhance standard infection prevention and control practices in hospitals, especially in emergency departments.
- Wash your hands often with soap and water for at least 20 seconds. Use an alcohol-based hand sanitiser that contains at least 60% alcohol if soap and water are not available.

WHO does not recommend any specific health measures for travellers. In case of symptoms suggestive of respiratory illness either during or after travel, travellers are encouraged to seek medical attention and share their travel history with their health care provider.

For healthcare workers and public health professionals, WHO has an online course titled Infection Prevention and Control (IPC) for Novel Coronavirus (COVID-19).

You can access the course through the following link: https://openwho.org/courses/COVID-19-IPC-EN.

This course provides information on what facilities should be doing to prepare to respond to a case of an emerging respiratory virus such as the novel coronavirus.

The WHO- China joint mission concluded on 24 February. The team has made a range of findings about the transmissibility of the virus, the severity of disease and the impact of the measures taken.

Findings of the team

- The team found that the epidemic peaked and plateaued between the 23rd of January and the 2nd of February, and has been declining steadily since then.
- They have found that there has been no significant change in the genetic makeup of the virus.
- They found that the fatality rate is between 2% and 4% in Wuhan, and 0.7% outside Wuhan.
- They found that for people with mild disease, recovery time is about two weeks, while people with severe or critical disease recover within three to six weeks.
- The team also estimate that the measures taken in China have averted a significant number of cases.

THE FUTURE OF COVID-19: DEDUCING STRUCTURE, DETECTING COV, GENETIC ENGINEERING, DEVELOPMENT OF MOUSE-ADAPTED COV, INACTIVATING COV

Deducing structure

However, neither vaccine nor drugs against CoVs are currently available. CoV contains a positive single-stranded RNA genome of ~30 kb, one of the largest among +RNA viruses.[7,8] To maintain the unusually large RNA genome, CoV encodes two replicase poly-proteins pp1a and pp1ab, which are broken down into 16

nonstructural proteins (nsps) via proteinase cleavage.[9,10] On which they form the membrane- associated replication-transcription complex (RTC). An RNA-dependent RNA polymerase nsp12 and a helicase nsp13 are the central components of RTC.[11,12] It is a multi-domain protein comprising of an N-terminal Cys/His rich domain (CH domain) and a C-terminal SF1 helicase core.[13] Nsp13 exhibits multiple enzymatic activities, including hydrolysis of NTPs and dNTPs, unwinding of DNA and RNA duplexes with 50-30 directionality and the RNA 50-triphosphatase activity.[14,15] To investigate the structure of CoV nsp13, we over-expressed the full-length CoV nsp13 (1-598aa) in insect cells and purified. Benefiting from the presence of an N-terminal zinc-binding domain with three zinc atoms, multi-wavelength anomalous diffraction (MAD) data at the zinc absorption edge was collected, which allowed the determination of the crystal structure of MERS-CoV nsp13.[13]

ELISA for detecting-CoV

Rapid laboratory diagnosis of CoV is the key to successful containment and prevention of the spread. Nucleic acid amplification test (NAAT), virus isolation, transmission electron microscopy, immunohistochemistry, and serological methods have been developed and used for CoV diagnosis.[16-21] "Gold standard" for CoV diagnosis is NAAT suggested by the World Health Organization (WHO), antigen capture ELISA assay for CoV can also be informative when NAAT is not available.[16,17]

Antigen capture ELISA to be more economical than NAATs for routine screening of CoV. To visualize the amplicons after agarose gel electrophoresis or during the qPCR thermal cycles, dyes like ethidium bromide (EtBr), SYBR Green, or Gel Red are used; while EtBr is a known mutagen, others are a relatively new addition to the market and extensive safety data is not widely available.[22] Finally, and most important, antigen capture ELISA can offer high sensitivity and specificity for CoV diagnosis in even early infection and animal samples. As the nasopharyngeal aspirate viral load from patients during acute infection are around 106 copies/mL and nasal samples in dromedaries are usually around 104-106 copies/mL, this test offers sufficient sensitivity for CoV diagnosis and screening.[23-25]

Genetic Engineering a Susceptible Mouse Model CoV induced Acute Respiratory Distress Syndrome.

Human-to-human transmission is often associated with close contact in the health care setting, but can also occur between family members within a house-hold.[26] Asymptomatic individuals pose a particular risk of transmission due to their unknown carrier status as demonstrated in the health care setting.[27]

Evaluating the toxicity and efficacy of novel CoV therapeutics require the availability of animal models that effectively recapitulate CoV pathogenesis during fatal cases of human infections. Therefore, the first question: What are the pathological features of a human infection? Limited histopathological findings from human autopsies indicate that fatal cases of CoV results from pneumonia initiated by infection of bronchiolar and alveolar epithelia of the lower respiratory tract (LRT).[28,29] High viral loads in tracheal aspirates from patients are also associated with severe pulmonary disease, which is indicative of actively replicating CoV in the LRT.[30]

Early studies in mouse, hamster, and ferret revealed that conventional small animal models were fully resistant to CoV infection and replication.[31-33] A seminal study identifying the MERS-CoV receptor as human dipeptidyl peptidase IV (hDPP4), and publication of the crystal structure of hDPP4 interacting with the receptor binding domain (RBD).[34] Dipeptidyl peptidase IV contact amino acids at the hDPP4/RBD interface are highly conserved among MERS-CoV-susceptible mammalian species (human, camel, and bat).[35] Although mouse, hamster, ferret, and guinea pig DPP4 orthologs exhibit high overall similarity to hDPP4, specific amino acid differences at the DPP4/RBD interface account for the inability of these species to support infection.[35-40] Over-expression of a mouse DPP4 (mDPP4) with changes in the contact residues at the DPP4/RBD altered cellular profiles from resistant to susceptible to MERS-CoV infection.[36,37,39] Dipeptidyl peptidase IV was identified as the major determinant of MERS-CoV tropism.

MERS-CoV mouse models

Zhao et al utilised a unique approach for producing susceptible mice that could replicate human isolates of MERS-CoV in the lungs by infecting mouse lungs with an adenovirus that constitutively expresses the full-length hDPP4 gene.[41] Transient expression of hDPP4 supported infection and replication with human strains of MERS-CoV in the lungs and indicated that this technology may be an effective rapid response platform for initial evaluation of emergent and pre-emergent viruses. However, pathology associated with a fatal MERS-CoV infection was not observed in the Ad-hDPP4 model, which limited the capacity to evaluate the efficacy of therapeutic countermeasures.[41]

Genetic engineering of mice would be necessary to develop preclinical MERS-CoV mouse models with respiratory phenotypes that reflected clinical outcomes in patients. Knock-in of full-length hDPP4 rendered mice susceptible to human isolates of MERS-CoV at low infection doses.[42-44] Knock-in mice exhibited severe pulmonary pathology and increased mortality; however, widespread constitutive expression of full-length hDPP4 resulted in high levels of MERS-CoV infection and replication in extra-pulmonary tissues.[42-44] In some studies, higher viral loads could be detected in the brain compared to the lungs.[43,44] Mice with infections of the central nervous system (CNS) exhibited encephalitis that

corresponded with the kinetics of mortality.[43] Currently, there is no evidence to support a CNS component associated with MERS-CoV pathogenesis in humans. Attempts to restrict hDPP4 expression to epithelial cells of the lungs using constitutive tissue specific promoters (e.g., cytokeratin K18) yielded outcomes similar to those observed with SARS-CoV mouse models, wherein high levels of MERS-CoV infection/replication were detected in the brains.[43]

Pascal et al employed Regeneron's Veloci Gene technology to replace sequences encoding nearly the entire mDPP4 genomic region with those encoding the exons/introns from the hDPP4 genetic region.[45] Retaining the mDPP4 5' and 3' genetic elements that regulate expression maintained inherent expression profiles of full-length hDPP4 in mice.[45] Infection with human isolates of MERS-CoV caused moderate respiratory pathology with mortality determined by euthanasia of mice at 20% weight loss.[45] Unfortunately, commercial restrictions limit the availability and use of this model to the broader scientific community. In addition to the concerns raised above, the first generation of mouse models was developed with the full-length hDPP4, which may alter the inherent physiological properties of the mouse.

DPP4 exists in two forms

- membrane anchored form on the surface of multiple cells types (e.g., B cells, T cells, NK cells, and epithelial cells to mention a few) and
- secreted form that can be identified in human serum.[46]

DPP4 interacts with and modifies heterologous protein molecules involved in nociception, neuroendocrine function, metabolism, cardiovascular function, immune regulation, and infection.[46] Interestingly, in one study adenosine deaminase (ADA) was demonstrated to block infection of MERS-CoV in tissue culture, indicating that the binding site on hDPP4 for ADA, and the MERS-CoV RBD, may overlap.[32] Consequently, introducing full-length hDPP4 into mice may skew innate immune mechanisms that could influence responses to therapeutic countermeasures.

Li et al recently developed a mouse model wherein the mDPP4 genomic region encompassing exons 10-12 were replaced with the respective genomic region from hDPP4, referred to as an hDPP4 knock-in model (hDPP4-KI).[47] Exons 10-12 encode contact amino acids at the hDPP4/MERS-CoV RBD interface that were able to support replication of human MERS-CoV isolates in the lungs, but did not elicit a mortality phenotype.[47] The hDPP4-KI model substantiate an earlier mouse model referred to as the 288-330+/+ model, which was designed with only two amino acid changes in mDPP4 to generate MERS-CoV susceptible mice.

Genetic engineering and implementation of the 288-330+/+ mouse model, combined with MERS-CoV adaptive evolution. Initial studies in tissue culture revealed that human and rodent cell types were resistant to MERS-CoV infection upon over-expression of mDPP4; however, over-expression of hDPP4 conferred permissivity to infection/replication.[37] The CRISPR/Cas9 genome editing technology became available for applications to modify mammalian genomes in vitro and in vivo.[48-50] Tissue culture adaption resulted in MERS-0 virus, which contained an RMR insertion and S885L mutation in the S2 region of the MERS-CoV spike protein.[51] Additionally, the MERS-0 virus replicated to higher levels in the lungs of 288-330+/+ mice, compared to human and camel MERS-CoV isolates.[51]

After 15 passages, a mouse-adapted MERS-CoV (MERS15c2) exhibiting a lethal respiratory phenotype in the 288-330+/+ mice was obtained.[51]

MERS-CoV reverse genetic system was used to generate an infectious clone of the mouse-adapted virus, icMERSma1.[51] Lethal respiratory pathology with icMERSma1 required high infectious doses (5x 106 Pfu). An additional 20 passages of icMERSma1 in 288-330+/- mice bore a novel mouse-adapted MERS-CoV that produced lethal respiratory disease at doses of 5 x 105 Pfu, and lung pathology associated with severe respiratory disease at 5 x 104 to 5 x 105 Pfu.[52]

This MERS-CoV model system (288-330+/+ mice and mouse-adapted MERS-CoV viruses) is now being employed to:

- understand complex virus-host interactions,[51,53-58]
- evaluate antibody-based therapeutics,[51]
- evaluate drug-based therapeutic countermeasures,[59]
- evaluate anti-MERS-CoV vaccines.[51,57]

For additional information there are a number of detailed reviews and book chapters describing the design and utilisation of the CRISPR/Cas9 technology for generating mouse models.[60,61]

Cockrell et al, Douglas et al, and Li et al, a number of mouse- adapted mutations were identified in genetic regions outside of the spike gene, which may have a significant influence on virus fidelity and evasion of host immune responses.[42-44]

It is important that the inoculum reaches the lower respiratory tract for a successful MERS-CoV infection.

Development of a mouse-adapted MERS coronavirus

In 2014, the first mouse model of MERS-CoV infection was developed, in which a recombinant adenovirus 5 encoding human DPP4 (hDPP4) was delivered to the lungs of mice.[62] The disease severity following MERS-

CoV infection in transgenic mice correlated with the cellular distribution and expression level of hDPP4.

However, the lethality was found to be secondary to overwhelming central nervous system (CNS) disease or multi-organ damage. This was also observed in mice transgenic for human ACE2 driven by the cytokeratin 18 promoter and infected with SARS-CoV.[63]

Two mouse-adapted (MA) strains of MERS-CoV were subsequently developed independently by serial passage of the HCoV- EMC/2012 strain in the lungs of the two humanised mouse models.[64-66] The resultant MERS-15 and MERSMA6.1.2 mouse-adapted MERS-CoV strains replicated to high titers in the lungs of the CRISPR-Cas9 genetically engineered mouse model and the hDPP4 knock-in mouse model, respectively. The respiratory disease that developed in both mouse models and the associated mortality shared similarities with severe cases of MERS.[65,66] Mouse adaptation was also successfully used to generate several SARS-CoV strains capable of modelling severe SARS-CoV lung disease in mice.[67-69] Thus, the adaption of the virus to enhance virulence in the mouse is a very useful approach to generate mouse models for coronavirus-associated lung disease.

While holding mice, make sure no pressure is applied over the throat area to avoid interference with respiration, monitor the health of mice before returning to the cage and record weights from the day of infection until recovery.

Animal euthanasia should follow the institution's Animal Care and Use guidelines. There may be differences in institutional requirements regarding when euthanasia is required based on weight loss.

Inactivating middleeast respiratory syndrome coronavirus

Proteins are the major effectors of cellular pathways and represent the dynamic expression of information encoded within the genome during infection. Protein driven cellular responses following infection can favor either viral clearance or spread; therefore, taking snapshots of total proteins isolated from infected cells over the course of infection can provide insights into their underlying molecular mechanisms of pathogenicity, and potentially even single out targets for pharmacological intervention.[70]

Metabolites are biomolecules that represent the level of homeostasis of cellular activities in a host.[71,72] Importantly, certain metabolites play key roles during the cellular responses to various viral infections such as signalling, initiating or resolving inflammation, or other immune related responses.[73] Therefore, metabolite levels can be profiled between healthy and disease states to not only understand the triggers of change but to also discover possible biomarkers in early disease stages.

Lipids have key functions in signalling pathways, energy storage, and the structural integrity of cell membranes. Lipid metabolism and cellular lipids are greatly affected by virus infections by inducing major lipid modifications within host cells through the production of convoluted membranes and double membrane vesicles (DMVs).[74-77] While it's clear that metabolites, proteins, and lipids play an important role in fully characterizing the MERS-CoV infection, the proteomic, metabolomic, and lipidomic sample manipulation of MERS-CoV outside of appropriate biosafety level (BSL) containment laboratories can take place only subsequent to pathogen inactivation.

MPLEx (metabolite, protein, and lipid extraction) protocol for the extraction of protein, metabolites, and lipids from a single sample that simultaneously inactivates the MERS-CoV virus.[78-80] Nakayasu et al. performed an integrative multi-omics study using a human lung epithelial cell line infected with MERS-CoV, which showed the impact of the viral infection on the host glycolytic pathway, different host metabolic pathways, and also global changes in lipid profiles induced by infection.[78] To illustrate the effectiveness of MPLEx on pathogen inactivation, Burnum-Johnson et al. showed complete inactivation of both bacterial and viral pathogens with exposed lipid envelopes, including MERS-CoV.[79]

The MPLEx method is a simple yet powerful protocol that can be applied for integrative multi-omic measurements while concurrently inactivating MERS-CoV (or other enveloped viruses). The multiple analyte samples obtained from MPLEx can be used across various instrument and data analysis platforms.

EVALUATION OF ACTIVATION AND INFLAMMATORY ACTIVITY OF MYELOID CELLS DURING PATHOGENIC HUMAN CORONAVIRUS INFECTION

Myeloid cells such as neutrophils and monocyte-macrophages are key immune cells that make up a large proportion of tissue infiltrating innate leukocytes following a pathogen challenge. Both neutrophils and inflammatory monocytes-macrophages (IMMs) are rapidly recruited to the site of infection and play crucial roles in the host defence against viral lung infections.[81,82] In addition to host protective function of myeloid cells during viral lung infections, several recent studies demonstrate their role in mediating cytokine storm and thus exacerbating the host immune response to virus infections.[82,83] The deleterious functions of neutrophils and IMMs are linked to dysregulated type I IFN (IFN-I) responses, particularly during high pathogenic virus infections.[84,85] IMMs and neutrophils also express increased levels of death receptors such as DR5 and FAS, and the interaction of these receptors with their ligands TRAIL and FASL, respectively, promotes airway epithelial and lung microvascular endothelial cell

death.[85-87] Additionally, excessive inflammatory cytokines and chemokines produced by IMMs and neutrophils impair antiviral T cell responses, leading to ineffective virus clearance and reduced survival.[84] A majority of the studies demonstrating the beneficial or detrimental effects of neutrophils and IMMs during viral lung infections enumerate percentages and total number and define activation status of the lung infiltrating myeloid cells using surface markers.[88] It recently showed spontaneous production of several inflammatory cytokines and chemokines by neutrophils and IMMs, which correlated with severe lung pathology and reduced survival in CoV infections.[84] Thus, the identification of specific inflammatory cytokines and chemokines produced by these cells will allow us to define their pro-inflammatory status and design strategies to control inflammatory responses.

Histopathologic evaluation of viral lung infection

Emergent coronaviruses such as severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV) have caused significant impacts on human health, especially during their initial outbreaks.[89,90] People infected with these coronaviruses often have significant lung disease that contributes to clinical morbidity and mortality.[91-93] Histopathologic examination and immunostaining (e.g., immunohistochemistry) of lung tissues are essential to better understand disease pathogenesis and evaluate novel treatments of these current (and future) virus outbreaks.[94-98]

CONCLUSION

Coronavirus being the deadly virus with no availability of vaccine and/or therapies, the preventive measures lie in providing knowledge about this virus to public through various means. Moreover the future lies in complete studies on this virus by using animal methods. Such animal models are useful to study the pathogenesis as well as immune response to it. The achievement will be by using genetic engineering as described. Detecting and assaying molecules are relevant to understanding the host immune response. The articles like this are a testimony to selflessness of the scientific and medical community and the noble cause to which they are committed.

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