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**Submission date:** 29-Jan-2021 05:13PM (UTC+0500)

**Submission ID:** 1496960390

**File name:** 2.\_PERSPECTIVE\_MOLECULAR\_IMMUNOPATHOGENESIS.docx (1.01M)

**Word count:** 2870

**Character count:** 25740

## PERSPECTIVE OF MOLECULAR IMMUNOPATHOGENESIS OF COVID-19 INFECTION

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### HIGHLIGHTS

SARS-CoV-2 increases the number of neutrophils as APC, suppresses IFN, increases the activity of Th1 / Th17, B cells, CD8 + and CD4 +, and causes cytokine storms especially pro-inflammatory cytokines which can increase respiration disorders and multi-organ damage.

### ARTICLE INFO

#### Article history

Received date

Revised date

Accepted date

#### Keywords:

Covid-19  
SARS-CoV-2  
Pathogenesis  
Immune Response

### ABSTRACT / ABSTRAK

Covid-19 is a type of Pneumonia that caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). When Covid-19 arise in Wuhan City China and rapidly spread throughout to the World, we need to learn how pathogenesis and immune responses occur in the bodies in more detail. Covid-19 is third Severe Respiratory Disease outbreak caused by the Coronavirus in the past two decades after Severe Acute Respiratory Syndrome (SARS) in the 2002 and Middle East Respiratory Syndrome (MERS) in the 2012. SARS-CoV-2 increases the number of neutrophils, suppresses IFN, increases the activity of Th1 / Th17, B cells, CD8+ and CD4+, and causes cytokine storms especially pro-inflammatory cytokines which can increase respiration disorders and multi-organ damage. This review tries to explain about pathogenesis and immune responses of Covid-19 to provide a reference in designing the appropriate immune intervention for treatment and therapeutic such as drug or vaccine based on the recent research progress SARS-CoV-2 and previous studies about SARS-CoV and MERS-CoV.

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## 1. INTRODUCTION

Coronavirus Disease 2019 (Covid-19) is a pathogenic viral infection caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that initially arise in Wuhan, Hubei Province, China and rapidly spread to the world. Initially, the cases arise in Wuhan's Hunan Seafood Wholesale Market which trade in fish and variety of live animal such as bats, marmots, and snake. The causative agent for the disease was identified from throat swab samples conducted by the Chinese Centre for Disease Control and Prevention (CCDC), and was subsequently named Severe Acute

Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Sequences-based analysis suggested that bat is key reservoir of SARS-CoV-2 and can be transmitted to humans.<sup>1</sup> Furthermore, transmission will occur from human to human as it is today.

On 30<sup>th</sup> January 2020, World Health Organization (WHO) declared that Covid-19 from Wuhan was to be a Public Health Emergency of the International Concern posing a high risk to countries. WHO announces this disease outbreak a pandemic diseases. It is due to the rapid increase in the number of cases outside China over the past 2 weeks that has affected a growing number of countries in the world.<sup>2</sup> There were 7734 cases have been confirmed in China on that day. In a number of counties also confirmed 90 cases.<sup>3</sup> On 30<sup>th</sup> March 2020, WHO confirmed that there was 638.146 cases with 30105 death in 203 countries in the World. <sup>4</sup> In Indonesia, Ministry of Health Indonesia confirmed that there is 1285 positive cases with 114 deaths and 64 recovering on 30<sup>th</sup> March 2020. <sup>5</sup>

Covid-19 symptoms appear after an incubation period of approximately 5.2 days. The period from onset the symptoms to death ranges is from 6 to 41 days with a median of 14 days. <sup>(6,7)</sup> This period is dependent on the age of the patient and status of immune system. The most clinical symptoms at onset of Covid-19 are fever, dry cough, and fatigue. The other symptoms include headache, sputum production, hemoptysis, diarrhea, dyspnea, lymphopenia, and bilateral lung infiltrates on imaging. <sup>7</sup>

The main problems of Covid-19 are high transmission and the absence of specific drugs and vaccines. For this problem, the immune system is an important aspect to support the host's self-defense and patient's recovery. This review may help in designing the appropriate immune intervention for treatment and therapeutic such as drug or vaccine in preventing more wide transmission and in development of the Covid-19 drugs based on the recent research progress SARS-CoV-2 and previous studies about SARS-CoV and MERS-CoV.

## 2. CHARACTERISTIC OF SARS-CoV-2

Coronaviruses (CoV) are enveloped viruses, non-segmented, and positive-sense single-stranded RNA (ssRNA) virus genomes in the size 26 to 32 kb, the largest known viral RNA genome. The virion structure consists of nucleocapsid which is covered by phospholipid bilayers (viral envelope). Nucleocapsid is composed by phosphorylated nucleocapsid protein (N) that bound together with genomic RNA. The viral envelope is composed by Enveloped protein (E) and Membrane protein (M). The membrane protein is a type III transmembrane glycoprotein that determine shape of viral enveloped.<sup>8</sup> The coronaviruses have the spike glycoprotein trimmer or Spike protein (S) that will bind to receptor to facilitated viral entry to host cell. The structure of CoV virion is shown in **Figure 1**.<sup>9</sup>

According to genotypically and serologically, coronavirus is divided into 4 genera such as  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$  Coronaviruses. The subfamily  $\alpha$  and  $\beta$  CoV usually causes Human CoV infections. SARS - CoV and MERS - CoV is included in  $\beta$  CoV. The SARS-CoV-2 is novel  $\beta$  CoV was named by the International Virus Classification Commission. <sup>(8,9)</sup>

## 3. TRANSMISSION AND CLINICAL CHARACTERISTIC OF COVID-19

SARS-CoV-2 rapidly is transmitted from human to human pathogen and causes a wide spectrum of clinical manifestations in Covid-19 patients. The major clinical manifestation of COVID-19 is similar to other human CoV infection. In general, SARS-CoV-2 is associated with high viral loads in upper respiratory tract secretion. Covid-19 is develop into Severe Acute Respiratory Infections and Acute Distress Syndrome especially in elderly, comorbidities, and immunosuppression patient.<sup>10</sup>

Human to human transmission of Covid-19 mainly occur via respiratory droplets when patient with coughs, sneezes or talks can infect another person via direct contact with the mucous membranes. The infection can also occur if a person touches an infected surface and then touches their eye, nose or mouth. The droplet do not travel that 2 meters and not linger than 3 hours in the air.<sup>11</sup>

Based on the presence of clinical features, Covid-19 is divided into 2 groups such as asymptomatic and symptomatic infection. Asymptomatic Covid-19 infection show positive SARS-CoV-2 nucleic acid testing of the pharyngeal swab samples but do not show the clinical feature until first day of continuous negative tests (1-21 days). Only 20.8% asymptomatic cases develop into symptoms cases during hospitalization such as fever, cough, fatigue and etc, 50% cases showed typical CT images of ground-glass chest and five (20.8%) presented stripe shadowing in the lungs. The remaining 29.2% cases showed normal CT image and had no symptoms during hospitalization (young patient estimated 14 years). However, no one cases develop into severe Covid-19 pneumonia or died. Asymptomatic carrier patient has potential to transmit the disease to others. This study also show that Asymptomatic Covid-19 carrier can transmit the virus into his family that develop to Severe Covid-19 pneumonia.<sup>12</sup>

According to some studies, incubation period of Covid-19 is 5 – 14 days following exposure and cause respiratory and systemic disorder.<sup>13</sup> The spectrum of symptomatic Covid-19 infection ranges from mild to critical. Mild stage is signed with high fever, dry cough, headache, fatigue, sputum production, lymphopenia, and diarrhea. Covid-19 infection cause cough (days 1 – 14), chills (days 1 – 9), high fever (days 7 – 9), fatigue (days 9 – 14), and shortness of breath (days 9-14). Severe stage is signed with dyspnea and hypoxia. Pathological finding of Covid-19 associated with acute respiratory disruption syndrome. Critical disease is signed with respiratory failure, shock, or multi-organ dysfunction. Covid-19 infection cause Acute Respiratory Distress Syndrome (ARDS) until death.<sup>13</sup>

The infection show laboratory features such as lymphopenia and elevated some molecules (liver enzymes, lactate dehydrogenase, elevated inflammatory markers, D-dimer, prothrombin time, troponin, creatine phosphokinase, and acute kidney injury. The laboratory testing show positive in Viral RNA PCR testing and Immunoglobulin M (IgM), and there is ground-glass chest, stripe shadowing in the lungs in CT Scan, and pneumonia in x-ray test.<sup>14,15,16</sup>

#### 4. MOLECULAR IMMUNOPATHOGENESIS OF COVID-19 INFECTION

Covid-19 is positive-sense single-stranded RNA (ssRNA) that entry to the patient via respiratory droplets when patient with coughs, sneezes or talks can infect another person via direct contact with the mucous membranes and touching infected surface the body (eye, nose or mouth).

Covid-19 S protein (envelope spike glycoprotein) will bind to ACE2 for SARS-CoV<sup>17</sup>, ACE2 SARS-CoV-2<sup>18</sup>, CD209L (a C lectin or called L-SIGN) for SARS-CoV<sup>19</sup>, DPP4 for MERS-CoV<sup>20</sup> then occur fusion between viral cell membrane and target cell.<sup>21</sup> Proteolytic cleavage occurs in S SARS-CoV protein in position (S2') mediated by membrane fusion and virus infectivity.<sup>22</sup> MERS-CoV has also evolved through the activation of two abnormal steps for furin membrane fusion.<sup>23</sup> In addition to membrane fusion, clathrin-dependent and clathrin-independent endocytosis also mediate the process of SARS-CoV virus entry into cells.<sup>24,25</sup>

After that viral RNA enters the cytoplasm of cells in the form of polyproteins and structural proteins which then replicates into new viral RNA. The cell will then be controlled by the structural protein SARS-CoV to form an envelope protein that will be inserted into the Endoplasmic Reticulum (ER) and Golgi apparatus while the nucleocapsid is formed by a combination of viral RNA genomes and nucleocapsid proteins. In the end the virus particles will be brought to Endoplasmic Reticulum-Golgi

Intermediate Compartment (ERGIC) for maturation and will then be removed by ERGIC with vesicles containing infectious viruses through vesicle vesicles which will docking with membranes so that the virus will be released again and ready to infect other healthy cells.<sup>17</sup>

Viral antigen entry stimulate immune response. Covid-19 viral antigen will be presented to the Antigen Presenting Cell (APC). Antigenic peptide will be presented by MHC (Human Leukocyte Antigen or HLA in humans) to the specific cytotoxic T lymphocyte virus. MHC Class I played the most role in this Ag Covid-19 presentation, although MHC class II also played a role.<sup>26</sup> The Covid-19 presentation antigen was not fully understood but can be associated with antigen presentation on SARS-CoV or MERS-CoV. Certain HLA polymorphisms have a risk of being susceptible to SARS-CoV infection, namely HLA-B \* 4601, HLA-B \* 0703, HLA-DR B1 \* 1202<sup>27</sup> and HLA-Cw \* 0801,<sup>28</sup> while HLA-DR0301, HLA-Cw 1502 and HLA-A \* 0201 has protection against SARS infection.<sup>29</sup> MHC class II molecules cause susceptibility to MERS-CoV infection,<sup>30</sup> such as HLA-DRB1 \* 11:01 and HLA-DQB1 \* 02:0. In addition, the Mannose Binding Lectine (MBL) gene polymorphism associated with antigen presentation is associated with susceptibility to SARS-CoV infection.<sup>31</sup>

SARS-CoV-2 stimulate innate and adaptive immune responses. SARS-CoV-2 leads to infection of ACE2 expressing target cells such as alveolar type 2 cells or other cell in lung. SARS-CoV-2 causes an increase in total neutrophils, reduces total lymphocytes, increases serum IL-6, and increases C-reactive protein. Increased neutrophils and decreased lymphocytes also correlate with disease severity and death. Covid-19 has higher plasma levels of many pro-inflammatory cytokines, IP-10, MCP-1, MIP-1A, and TNF $\alpha$ .<sup>2</sup> that show highly pro-inflammatory conditions in the disease progression and severity. Activation of neutrophil as Antigen Presenting Cell (APC) increase Th1/Th17 expression. Th1/Th17 is induced adaptive response by increase specific antibodies production. Viral antigen may decrease antiviral IFN responses resulting in uncontrolled viral replication whereas IFN is effective innate immune response against viral infection and induce effective adaptive immune response. Type I IFN suppression and hyper pro-inflammatory cytokine production be the basis of viral infection treatment including SARS-CoV infection.<sup>32</sup>

In adaptive immune response, Covid-19 viral antigen will stimulate humoral and cell mediated immunity by B cells and T cells. B cells will form IgM and IgG anti SARS-CoV. IgM will disappear on the 12<sup>th</sup> day while IgG will last a long time in the body which will function as a protector against infection with the same virus strain.<sup>33</sup> IgG anti SARS-CoV is S-specific and N-specific.<sup>17</sup> In general, Th1 plays a dominant role in an adaptive immunity against viral infections. Specific Th1/Th17 may be activated and contributes to exacerbate inflammatory responses. B cells/plasma cells produce SARS-CoV-2 specific antibodies that may help neutralize viruses. In previous study showed the peak of specific IgM at day 9 after disease onset and the switching to IgG by week 2. Whether the titer of specific antibody correlates with disease severity remains to be investigated.<sup>32</sup>

In cellular immune response, the number of CD4<sup>+</sup> and CD8<sup>+</sup> cellular immunity in peripheral blood will drop significantly in SARS-CoV-2 infection.<sup>34</sup> Patients recovering from SARS-CoV will have CD4<sup>+</sup> and CD8<sup>+</sup> memory T cells that last for 4 years so that when there is repeated viral exposure the body will be able to produce IFN- $\gamma$ .<sup>35</sup> In some patients the specific T cell memory of SARS-CoV can still be identified.<sup>36</sup> CD8<sup>+</sup> T cells specific to MERS CoV are also found in mice that are infected with the virus.<sup>36</sup> In general, CD8<sup>+</sup> T cell responses are more frequent with greater magnitude than CD4<sup>+</sup> T cell responses in SARS Coronavirus. Strong T cell responses correlated significantly with higher neutralizing antibody while more serum Th2 cytokines (IL-4, IL-5, IL-10). In MERS-CoV infection, early rise of CD8<sup>+</sup> T cells correlates with disease severity and at the convalescent phase, dominant Th1 type helper T cells are observed. In an animal

model, airway memory CD4+ T cells specific for conserved epitope are protective against lethal challenge and can cross react with SARS-CoV and MERS-CoV. Th1 type and CD8+ T cell are keys for successful control of SARS-CoV and MERS-CoV and probably true for SARS-CoV-2 as well to suppress lung pathogenesis.<sup>32</sup>

The leading cause of death in Covid-19 infection is Acute Respiratory Distress Syndrome (ARDS) and multi-organ dysfunction. ARDS is the leading cause of death. This ARDS is an immuno-pathological event from SARS-Cov-2, SARS-CoV and MERS-CoV infections.<sup>33</sup> More patients also developed lymphopenia and pneumonia with characteristic pulmonary ground glass opacity changes on chest CT. Covid-19 infection also show cytokine storm. Cytokine storm is inflammation that cannot be controlled and is very deadly due to the body's response due to the large production of inflammatory cytokines such as (IFN- $\alpha$ , IFN- $\gamma$ , IL-1 $\beta$ , IL-6, IL-12, IL-18, IL-33, TNF- $\alpha$ , TGF- $\beta$  etc.), as well as some chemokines such as (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10 etc) produced by several immune effector cells produced by SARS-CoV infection.<sup>38,39,40</sup> For example in patients with severe MERS-CoV infection, an increase in the production of cytokines IL-6, IFN- $\alpha$ , CCL5, CCL8 and CXCL-10 in their serum compared with patients who have mild to moderate symptoms.<sup>41</sup> The production of pro-inflammatory cytokines mentioned above causes the patient's body to experience ARDS which can cause multiple organ failure (MOF) and ARDS until death. The presence of lymphopenia and cytokine storm may important role in Covid-19 pathogenesis. The Cytokine storm can initiate viral sepsis and inflammatory-induced lung injury which lead to other complications including pneumonitis, ARDS, respiratory failure, shock, multi-organ failure and potentially death.<sup>34</sup> Immune response to SARS-CoV-2 infection based on clinical manifestation approach, clinical laboratory test results, and studies of immune response on SARS-CoV and MERS-CoV can be shown in **Figure 2**.

SARS-CoV and MERS-CoV use various strategies in order to survive against host immunity. Microbes have pathogen-associated molecular patterns (PAMPs) that can be recognized by pattern recognition receptors (PRRs). SARS-CoV and MERS-CoV can induce the production of double membrane vesicles containing little PRRs and can replicate in these vesicles, so that SARS-CoV dsRNA can avoid detection of the host immune system.<sup>42</sup> Hosts can produce IFN- $\alpha$  and IFN- $\beta$  which can protect the effects of SARS-CoV infection.<sup>43,44</sup> Another corona virus, MERS-CoV, has a protein accessory molecule 4a that can inhibit MDA5 activation to induce IFN production by interacting directly with dsRNA.<sup>45</sup> MERS-CoV also has ORF4a, ORF4b, ORF5 and viral protein membranes that can inhibit the transport of IFN regulatory factor 3 (IRF3) and inhibit the activation of IFN- $\beta$  promoters.<sup>46</sup> MERS CoV can also hold genes that play a role in the presentation of Ag viruses.<sup>47</sup>

## 5. CONCLUSION

Specific studies on the immune response to SARS-CoV-2 are still developing. Various study approaches can be carried out by looking at the clinical manifestations that emerge, the results of examinations and literature review from their predecessors, namely SARS-CoV and MERS-CoV. So far, it can be concluded that molecular studies related to SARS-CoV-2 immunopathology states that SARS-CoV-2 increases pro-inflammatory cytokine production, suppresses IFN, increases neutrophil count, increases Th1 / Th17 expression, B cell response, and CD8 + and CD4 + responses. Cytokine storms are known to be a trigger for serious respiratory problems and multi-organ damage that can cause death.

## ACKNOWLEDGEMENT

This work was supported by STIKES Rumah Sakit Anwar Medika.

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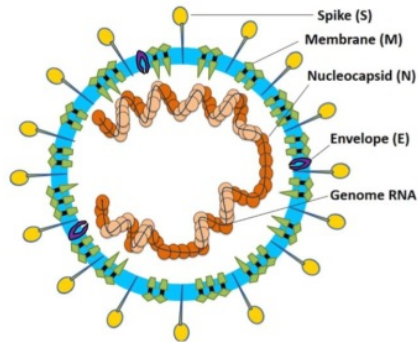
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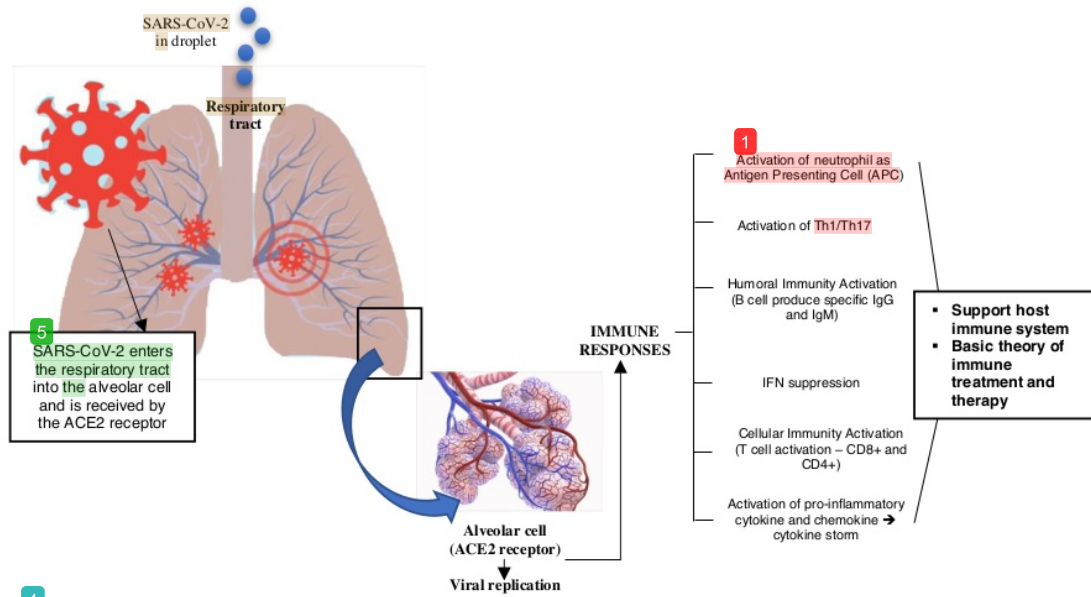
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Picture



7 **Figure 1. The Structure of Coronavirus (CoV) Virion**

6 Source: Li *et al.*, 2020



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