Title: COVID-19 in a Histopathological and immunological view

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Abstract

The virus that spread in all over the world and made such a pandemic, Severe Acute Respiratory Syndrome (SARS) corona virus-2; SARS-COV-2 for short. It is another member of the corona virus family which caused the 2019 corona virus; COVID-19. The global research focus is on how to tackle this disease by trying to find a treatment and a vaccine to prevent further infection. Such efforts has come via the symptoms from COVID-19 patients. Histopathological changes in these patients is one of the areas that is highly recommended for the researcher in order to find out the mechanism of action for this virus. In another hand, one of the significant parameters that all COVID-19 patients share is the cytokine storm. Researchers has extensively studied this field due to the tissue damage that is caused by the pro-inflammatory mediators. However, correlating both histopathological changes and their immunological background is still poorly studied. Therefore, in this review, we try to shed a light on the current knowledge that is available and analyzing both area to find possible mechanisms that lead to the tissue damage and organ failure which enhance the severity of COVID-19 in patients.

Introduction

In this review we collect and display all the Immunohistological changes that mentioned in recent literature of the coronavirus disease to create guidelines and recommendation .Many researchers recorded a set of histological changes that occur in different organs of the body when infected with COVID-19 and some histological changes were similar and agreed upon in the researchers 'results and some of the tissue changes were not agreed upon by the researchers (in another word its controversay), and the reason for this may be due to the lack of histological studies that were conducted on the patients of COVID-19, and therefore we will review the most important histopathological changes resulting from the injury of COVID-19 .

Histopathological changes

COVID-19 disease is one of the viral diseases that affect the respiratory system and that the most pathological tissue changes have been recorded in the lungs. The histopathological changes in the lungs varied with patients , but they were all consistent with diffuse alveolar damage(Fox *et al.*, 2020).Some researchers have considered that the formation of hyaline membranes and vascular congestion mark as it in acute stage (Fox *et al.*, 2020, Tian *et al.*, 2020).The acute stage of diffuse alveolar damage characterized by numerous hyaline membranes without evidence of interstitial organization (Barton *et al.*, 2020).(Fox *et al.*, 2020) also mentioned that the scattered hyaline membranes could be seen, as well as fibrin deposition, highlighted by trichrome stains.

While other researchers (Xu *et al.*, 2020) observed neither fibrinous exudate nor hyaline membrane formation and there were a large number of monocytes, a few lymphocytes and variable numbers of red blood cells in a few alveolar spaces. Additionally, multinucleated syncytial cells with atypical enlarged pneumocytes were identified in the intra-alveolar spaces, showing viral cytopathic like changes.

Immune response to SARS-COV 2

Understanding the mechanism of the virus entrance to the host cell will widen the current research on COVID-19.To do so, there is a need to understand the host immune responses towards this virus. Therefore, the focus in this section would be on the innate and adaptive immune system that is triggered by SARS-COV-2. The disease symptoms are described in detailed elsewhere (Jin *et al.*, 2020b, Jin *et al.*, 2020a).

Innate immune response to SARS-COV-2:

From an immunological point of view, COVID-19 patients developed the following parameters; elevated pro-inflammatory cytokines such as IL-2, 1L-6, IL-7, IL-10, G-CSF, MCP1 and TNF-α. Which is why is so called "cytokine storm" due to the significant increase in their levels (Huang *et al.*, 2020). This leads to the disease progression and severity. Other reports showed increased neutrophil counts, reduced total lymphocyte (lymphopenia) and increased of C-reactive protein (CRP) levels alongside with the cytokine storm (Qin *et al.*, 2020). In general, innate immune response to viral infection depends on Interferon 1; IFN1 and its downstream signaling which controls the virus from being replicated and induce the adaptive immune response(Andreakos and Tsiodras, 2020).

Gene sequencing researches showed that SARS-COV-2 has 90% homology to SARS-COV (Chen and Zhong, 2020) also seems to share the host receptor which is Angiotensin converting enzyme -2 (ACE-2)(Verdecchia *et al.*, 2020). This receptor is expressed in in type 2 alveolar cells. In this context, it is reported that SARS-COV infects macrophages and T-cells, both cells mediate the pathogenicity of SARS-COV(Hu *et al.*, 2012). This suggests that SARS-COV-2 might do the same. Further study in this line could add to the knowledge around the virus pathogenicity. Other research reported that ACE2 is expressed on the ciliated and goblet cells in the airways (Sims *et al.*, 2005, Sungnak *et al.*, 2020). It is recorded that ACE2 is also expressed by cardiac

cells which may explain the cardiovascular complications in some patients (Zhang *et al.*, 2020). However, other receptors might be involved in the entrance of SARS-COV-2 to the host cells (Li *et al.*, 2020). After internalization, the virus starts to interfere with the infected cell signaling in order to proliferate, whilst the infected cell undergo apoptosis .here, we have to mention that one of the strategies that the virus uses to avoid itself from being recognized by the immune cells is provoking the cells from releasing the major histocompatibility complex MHC molecules to its surface; one of the host mechanisms to make the immune cells recognize the viral infected cells. After this, the virus particles is released to the intercellular microenvironment which triggers the immune cell (macrophages, dendritic cells, monocytes, neutrophils) recognition via pattern recognition receptors PRRs. These cells in turn release their cytokines such as IL-6, TNFα, IL-1β and other cytokines. This release of pro-inflammatory cytokines enhance the adaptive immune cells to be involved.

Adaptive immune response to COVID-19

The second line of the immune response to the virus is the acquired immunity. Two main cells are involved in this response, T- lymphocyte and B-lymphocyte. In this context, CD4+ T cells and CD8+ cell phenotypes are the main cells involved in the anti-viral response (Channappanavar *et al.*, 2014). However, it seems that the virus escape from this mechanism due to the T-cell infection itself and undergo apoptosis which is the reason of lymphopenia in COVID-19 patients (Liu *et al.*, 2020).

As mentioned earlier in this paper, that IFN-α is one of the main cytokine mediators that is responsible for the virus clearance from nearby cells (released by the infected cells). The over-production of the cytokine and its continues release to the late stages worsen the pathogenicity of COVID-19. This

uncontrolled local and systemic inflammatory response leads to immune dysregulation which is associated with the mortality.

Because alveolar cells are the first main target cells for the SARS-COV-2 virus, therefore, first organ that is affected by the cytokine storm would be the lung. For example, one study revealed that infiltration of both monocyte and lymphocytes were seen in the visceral pleura and near the alveolar septa. This put together the immune dysregulation and histological changes in one content (Zeng *et al.*, 2020). The same study immune-histopathology part showed pneumocyte hyperplasia and evidence of macrophage like cells in the alveolar space which might be another correlation in COVID-19 pathogenicity.

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