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Letter to Editor A SCITECHNOL JOURNAL

Melanoma Differentiation Associated Protein 5: The Target of Sars Cov-2 in the Way to Acute Respiratory Distress Syndrome

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Abstract

As a global threat, COVID-19 continues to be the leading problem of every nation to be solved. Severe pulmonary involvement resulting in Acute Respiratory Distress Syndrome (ARDS) seems to be the major pathophysiological event in the mortality of Covid-19 as in infections caused by other betacoronaviruses. Although there are tremendous studies all over the world to prevent deaths from COVID-19, there is no antiviral drug with proven high efficiency yet. Day by day, we learn more about the SARS Cov 2, a single-stranded RNA virus causing COVID-19, but what we already know more about is the host the virus infects. So, as the interaction between the Sars Cov 2 and the host is getting clearer, specifying the ways the host immune system reacts to the virus properly or improperly and developing strategies to modulate immune responses in a way that would not result in the catastrophic lung injury called ARDS would be possible. In that sense, studies examining the immune responses to COVID-19 are of particular importance, opening the way to host-directed therapies.

Keywords: Covid-19; Sars cov-2; ARDS; Melanoma differentiation associated protein 5; Clinically amyopathic dermatomyositis

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Host cells recognize foreign invaders such as viruses by sensing their several components through Pattern Recognition Receptors (PRRs) deployed in different compartments. Such receptors sensing RNA viruses are Toll-Like Receptors (TLRs) localized to plasma or endosome/lysosome membranes, and Retinoic acid-Inducible Gene-1-like receptors (RIG-Is) or Melanoma Differentiation Associated protein 5 (MDA5) in the cytoplasm . As a cytosolic PRR, MDA5 has the potential to sense ds-RNAs produced by SARS CoV-2 during its replication with the resultant downstream Interferon Regulatory Factor 3 (IRF3) activation and interferon-beta stimulation. Interferon-mediated antiviral responses are crucial to host antiviral defense. Corona viruses have host PRR evading mechanisms as a family feature. SARS CoV, as an example, has been associated with interference of early interferon responses in cells, which has been linked to uncontrolled pro-inflammatory cytokine surges in myeloid cells as well as hyper activated inflammatory monocytes and macrophages that accumulate in the lungs, resulting in severe injury and ARDS. Recent studies suggest that dysregulated interferon response is a main contributor to COVID mortality. Ineffective interferon response to Sars Cov 2 due to inborn genetic errors in interferon system or anti-interferon auto anti bodies has been shown to be responsible for 14% of the life-threatening consequences of COVID infection. Another specific cause of inadequate interferogenic response may be defective MDA5 sensing of SARS Cov 2 due to dysfunctional MDA5. This may be an underlying factor for ARDS in covid and anti-MDA5 antibody positive Clinically Amyopathic Dermatomyositis (CADM).

Interstitial pneumonia caused by COVID-19 is typically characterized by peripheral focal, multifocal, or diffuse ground-glass opacities or consolidations that can affect both lungs. The pathologic examination findings of ARDS in COVID-19 patients are Diffuse Alveolar Damage (DAD) with hyaline membrane formation and interstitial mononuclear inflammatory infiltrates in the lung. Although these radiological and pathological findings resemble those seen in SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome), they are surprisingly shared by anti-MDA5 antibody positive CADM, which also has been shown to be complicated suddenly with severe lung destruction with fatal respiratory failure despite initiation of corticosteroid therapy. Patients with anti-MDA5 antibody positive CADM have been reported to rapidly progress to Interstitial Lung Disease (ILD), demonstrating random ground-glass shadows and peripheral lung consolidations by computed tomography of the lung and hyperferritinemia even without any skin manifestation of dermatomyosistis. A viral etiology, especially coxackieviruses belonging to picornaviruses that are targeted by IFIH1/MDA5, has been associated with anti-CADM-140 antibodies, which are specific to acute ILD in CADM patients and identify MDA5. Nishina et al implicated in seasonal (predominantly from October to March) and residental clustering at disease onset of anti-MDA5-associated ILD. Although this suggests virus induced

deterioration, examining whether prior virus infection leads to the beginning of quickly increasing anti-MDA5-associated ILD is a future goal.

Gautret et al. studied macrolides in their COVID-19 patients, dividing them into three groups: the hydroxychloroquine plus azitromycin group, the hydroxychloroquine only group, and the no drug (placebo) group. On day 6, all (100%) patients treated with hydroxychloroquine in combination with azithromycin showed PCR-based virological cure compared with a 57.1 % cure rate in patients treated with hydroxychloroquine alone and a 12.5 % cure rate in patients enrolled in placebo. This augmented effect in the first group may be secondary to a pleiotropic MDA5-dependent antiviral interferojenic effect of azitromycin as Mendzel et al. suggested for viral infections other than coronaviruses in patients with asthma, but the benefit of azitromycine in COVID-19 has not been confirmed in subsequent trials and the drug has been linked with QT interval prolongation, especially when used with hydroxychloroquine.Interferon treatment has been trialed for compensation of defective interferogenic response in COVID-19 patients. Dastan et al. found subcutaneous IFN-beta-1a administration successful in combination with hydroxychloroquine and lopinavir/ritonavir in the management of COVID-19 [14]. Rahmani et al. showed that IFN-beta-1b 250 mcg subcutaneously every other day for two consecutive weeks was effective in shortening the time to clinical improvement without serious adverse events in patients with severe COVID-19. In a recent trial by Khamis et al., no differences in clinical outcomes were found between favipiravir plus inhaled interferon beta-1b and hydroxychloroquine in adults hospitalized with moderate to severe COVID-19 pneumonia. IFN seems to be a significant antiviral defense mechanism and immune modulator in COVID 19, but the timing of its response or administration is critical in determining its success. In line with this, Wang N et al. found an association between early IFN use and significantly reduced in-hospital mortality. However, no important clinical benefit of IFNs was observed in moderately ill COVID-19 patients and late administration of IFN could be associated with a longer hospital stay.

We hypothesize that dysfunctional MDA5, caused by SARS CoV-2 specific innate immune evasion factors or blocking antibodies against MDA5, with a resulting insufficient interferon response, is the root cause of immune dysregulation that can lead to the development of sudden interstitial immune pneumonia and ARDS. Targeting MDA5 function may be an appropriate strategy to develop treatments to protect the host from immune-mediated ARDS in both patients with COVID-19 and CADM. Further studies examining the sensing of SARS CoV-2 by specific host cell PRRs (especially by MDA5), the prevalence of anti-MDA5 antibodies in patients with ARDS associated with Covid-19 or CADM, and the functional status of MDA5 in both patients with ARDS associated with Covid-19 or CADM are urgently needed

Conflict of Interest

The authors have no financial and personal relationships that could influence the work presented in this manuscript.