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How does SARS-CoV-2 Manipulates the Immune System? Critical Role of Th1, Th2, Th17 Responses

SARS-CoV-2 Bağışıklık Sistemini Nasıl Yönlendiriyor? Th1,Th2,Th17 Yanıtlarının Önemi

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To the Editor,

It is well known that viruses utilize several virulence mechanisms including manipulation of the host immune system. Human coronaviruses (HCoVs) may inhibit interferon responses, induce apoptosis, and manipulate various intracellular pathways.[1] Here, we discuss the successful and unsuccessful strategies of immune systems of COVID-19 patients. Based on observations from aged and younger patients, we conclude that, in general, patients who can respond to the virus with an early and adequate Th1 response have better chances of survival. Those who cannot produce enough interferon I (IFN I) switch to Th2 response profile, which produce complicated consequences. We suggest that treatment of older patients that are susceptible to severe form of the disease with IFN-I on the onset of the disease, should be beneficial.

There are several *in-vitro* studies demonstrating IFN-I suppressive effect of SARS-CoV.[2] Moreover, a recent study has shown that SARS-CoV-2 can inhibit IFN-I production via ORF3b protein.[3] The suppression of IFN-I response is crucial for viral pathogenesis. The capability of SARS-CoV-2 to suppress IFN-I, should likely attenuate the viral clearance mechanisms, leading to increased viral survival rate, which in turn can facilitate other virulence mechanisms of the virus.[4] Additionally, suppression of IFN-I response also impairs the adaptive immunity at later stages of the disease. Impaired IFN-I response leads to diminished Th1 subset and down regulation of cytolytic activity of $CD8^+$ T and memory Th cells. Moreover, lack of adequate IFN-I action results in the absence of inhibitory effects of Th1 on Th2 and Th17 development.[5] Therefore, IFN-I suppression can be considered as the first and possibly the most important strategy of SARS-CoV-2.

Defective viral clearance leads to disease progression and the formation of diverse manifestations, such as cytokine dysregulation and ALI/ARDS-like symptoms, which are mainly orchestrated by various viral virulence mechanisms. HCoVs, especially SARS-CoV-1, are capable of inducing proinflammatory cytokine production, such as TNF-α, IL-1β, IL-6, and IL-8, via activation of NF-κβ, MAPK and inflammasome pathways.[1,6] Cytokine composition observed in COVID-19 patients suggests that SARS-CoV-2 also causes proinflammatory response through similar pathways. Severity of the disease is associated with lymphopenia, neutrophilia, increased IL-1, TNFα, IL-6 and IL-10 cytokine levels and decreased IFN-γ production by $CD4^+$ T cells.[7–9] This suggests that, along with increased proinflammatory cytokine levels, SARS-CoV-2 also causes an impaired Th1 response and lymphocyte homeostasis in severe cases. IL-6 has negative effects on Th1 differentiation and T cell activation.[8,10] Moreover IL-6 and TNF-α levels are negatively correlated with total T cell counts in patients with COVID-19.[8] Besides IL-6, IL-1β and Transforming Growth Factor-β (TGF-β) induce Th17 subset differantiation.[10] This suggests that the cytokine

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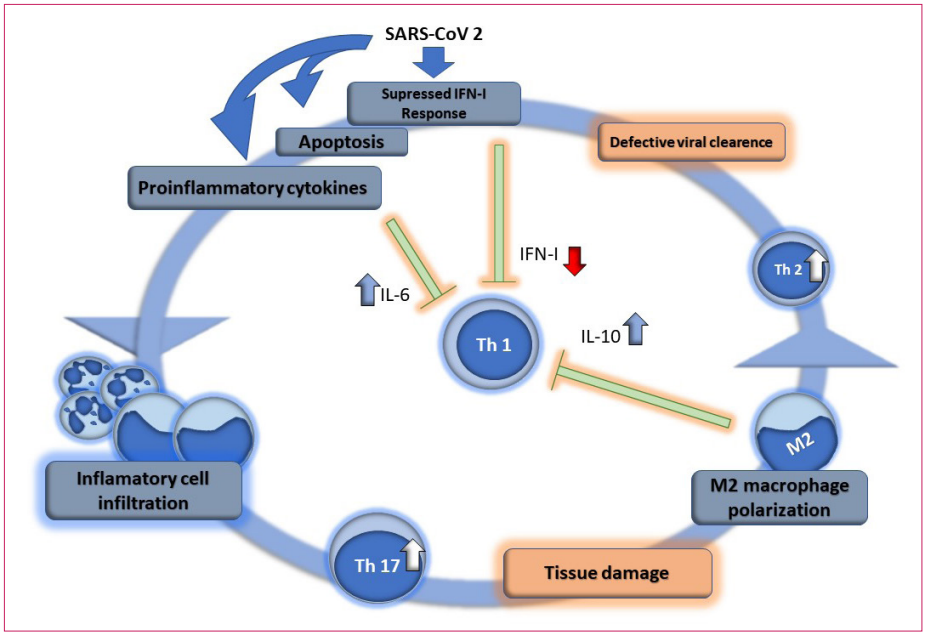

Figure 1. Consequences of suppression of Th1 response in COVID-19

Suppression of IFN-I response and induction of proinflammatory cytokines, leads to an excessive Th17 response which associates with neutrophils and macrophages. This uncontrolled inflammation causes tissue damage along with virus induced apoptosis. Accumulation of cell debris and apoptotic bodies leads to M2 macrophage polarization. Resulting Th1/Th2/Th17 imbalance associated with initially low IFN-I, high IL-6 and IL-10 levels lead to further suppression of Th1 response and defective viral clearance.

profile induced by SARS-CoV-2, may lead to Th17 activation. This view is supported by neutrophilia and high granulocyte colony-stimulating factor (GCSF) levels that is in association with severe disease.[7] With the unbalanced adaptive immune response associated with decreased Th1 activity, further impairs the anti-viral immune response.

With the failure to control the infection and progression of the disease, excessive inflammatory response leads to tissue damage and consequently ALI/ARDS in later stages.[11] Along with these factors that cause disruption of tissue homeostasis, another known virulence factor of HCoVs should be included in the equation, namely induction of apoptosis.[1] Infection of alveolar epithelial cells (AEC) and alveolar macrophages, apoptotic bodies accumulate in alveoli.[12] Moreover, both AEC II and alveolar macrophages are involved in cleaning of apoptotic AEC II cells.[13] Infection of these scavenging cells can possibly cause further accumulation of apoptotic bodies. Abundance of apoptotic bodies and tissue damage may stimulate the differentiation of macrophages towards M2 subtype, especially in the late phase of the disease. They are the main cells involved in scavenging of apoptotic bodies and associated with resolution of inflammation, tissue repair and secretion of low IL-12 and high IL-10 levels.[14] Thus, M2 macrophage activation could explain high IL-10 level found in severe patients. Moreover, it was shown that peripheral blood monocytes of COVID-19 patients and alveolar macrophages secrete IL-10.[15,16] M2 macrophage activation and elevated IL-10 levels further impair the protective Th1 response, and consequently the viral clearance. We speculate that the lack of a timely and sufficient Th1 immune response, may drive the immune system towards Th2 immunity in the end stage of disease. It has been suggested that SARS-CoV-1 infection shifts M2 macrophages phenotype to a more M1-like phenotype in-vivo.[17] However, there are also opposing views on this topic.[18] A recent study suggest that severe SARS-CoV-2 causes M2 macrophage polarization and subsequent T cell exhaustion.[19]

Host related factors play important role in viral clearance. In SARS-CoV-2, severe outcome is associated with old age, hypertension, diabetes, obesity, chronic obstructive pulmonary disease (COPD) and active smoking but not allergic diseases.[7] Active smoking, COPD and diabetes have negative effects on both AEC physiology and alveolar surfactant levels. Asthma patients have high lung surfactant levels.[20] It is known that surfactant protein A and D, have various anti-inflammatory effects. It was found that Sp-D deficiency causes increased NF-κβ activity, matrix metalloproteinase production by alveolar macrophages and secretion of IL-1β, IL-6 and MIP-2 in response to LPS in animal models.[21,22] Thus this may explain why asthma was not found to be a predisposing disease compared to other lung pathologies.[21] Diabetes is also associated with increased NF-κβ activity and proinflammatory cytokines production such as IL-6, IL-1β and TNF-α.[23] Thus, impaired AEC physiology, deficient alveolar surfactant levels and proinflammatory conditions might be enhancing the immune system manipulations of SARS-CoV-2.

In conclusion, we think that the most important and maybe the first step of viral virulence strategy is the suppression of IFN-I and this is avoidable. The suppression of IFN-I production increase apoptosis and uncontrolled production of proinflammatory cytokines which ultimately leads to induction of Th-17 and inhibition of Th1 responses. With the impaired viral clearance and activated Th17 response cause considerable tissue destruction. End stage of the disease is characterized with M2 macrophage polarization, Th2 based immune response and secretion of high amounts of IL-10. (Figure 1). Thus, we recommend the administration of IFN-I, which is successfully employed in clinics for multiple other indications for decades, in the treatment of patients that are prone to severe diseases. Immediately after COVID-19 diagnosis, IFN I treatment for 1–2 weeks is expected to restore the proper Immune response and save lives of the patients.

After submission of our manuscript, more publications appeared in the literature which supports treatment of COVID-19 patients with interferons. Zhou Q, et al. found that inhaled IFN-α2b treatment of COVID-19 patients accelerated viral clearance and decreased IL-6 serum levels. [24] Also, there are several ongoing clinical trials using IFNs such as inhaled IFN-beta in COVID-19.[25,26]

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