Dear Editor

To establish effective vaccines and developing appropriate therapeutic interventions in COVID-19, a full understanding of the immune response against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is critical. The host immune system is dramatically perturbed by SARS-CoV-2 infection and the integrity of the host’s homeostatic response plays an important role in the pathogenesis of COVID-19 (1). Immune checkpoint inhibitors (ICIs) are suggested to play an important role in the pathogenesis COVID-19 disease. ICIs have been used extensively in the treatment of cancers where they upregulate the host immune response against cancer cells. Important side effects include pneumonitis (2). Programed cell dead-1 (PD-1) is an important target of ICIs as it inhibits immune cell functions and is an exhaustion marker for immune cells. PD-1 is expressed on activated CD8+ T cells, B cells and NK cells in the setting of chronic antigen exposure. Binding of PD-1 and its ligand PD-L1 or PD-L2 on host tissues leads to the inhibition of T cell receptor (TCR) signaling and CD28 co-stimulation (3, 4). In chronic infections disease, PD-1 is expressed in exhausted TCD8 cells following demethylation of its promoter allowing DNA binding and gene activation by the FOXO1 transcription factor (5). In cancer, due to increasing the tumor cells changes and tumorigenic pattern, PD-1 expression is enhanced by activation of the c-FOS subunit of AP-1 (6). Aberrant PD-1 expression and activity, as a regulator of the immune response, may have both a beneficial and harmful impact on the immune system during cancer pathogenesis (7).

Recent studies demonstrate upregulation of PD-1 and PDL-1 on immune cells of COVID-19 patients suggesting a possible role for T-cell exhaustion in promoting severe COVID-19 (8). Increased expression of PD-1 on T- and NK cells of patients with COVID-19 further implicates T-cell exhaustion and suggests that ICIs may be a useful approach against SARS-CoV-2 infection as it will result in an upregulation of the immune response to the virus. In addition, increased PD-L1 expression has been reported on many inflammatory cells in severe COVID-19 patients (9). Interestingly, this included enhanced expression of PD-1 on basophils and eosinophils that correlated with COVID-19 severity (9). One possible reason for the overexpression of PD-1 in COVID-19 patients is the cytokine storm, which leads to CD8+ T-cell exhaustion. In severe COVID-19 patients, blood levels of proinflammatory cytokines such as IL-6, IL-17, and TNF-α, are significantly elevated together with an increased activity of the host immune system (10). These mediators are able to trigger an up-regulation of PD-L1 on the...
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surface of immune cells via well-known signaling pathways including PI3K/Akt and nuclear factor-κB (NF-κB) signaling to induce apoptosis (11). Further evidence that immune cell exhaustion may be important in severe COVID-19 is provided by the fact that the anti–IL-6 monoclonal antibody tocilizumab increased CD8+ T-cell frequency and function in COVID-19 patients (12).

Thus, blockade of PD-L1/PD-1 could be an approach that restores CD8+ T-cell numbers and functions. Moreover, anti-inflammatory cytokine therapies may also be used to reduce the inflammatory status and restore CD8+ T cell functions. For example, IL-15 has been suggested for the treatment of COVID-19 patients (13). Understanding the axis of a cytokine storm/PD-L1/PD-1/CD8 T-cell exhaustion may provide a rationale for the development of novel therapeutic interventions in COVID-19 disease.

In summary, in COVID-19 pathogenesis proinflammatory cytokines bind to their receptors on immune cells and produce positive signals, which increase the expression of PD-L1. PD-L1 binds to PD-1 on CD8+ T cells to produce inhibitory signals, which block the ability of CD8+ T cells to release cytotoxic mediators such as perforin and granzyme B and in parallel causes apoptosis of CD8+ T cells. Therefore, blockade of proinflammatory cytokines and activated signaling pathways together with ICIs may be of therapeutic use in patients with severe COVID-19. In conclusion, although the mechanism for the induction of PD-1 and other ICI family members in COVID-19 patients may differ from that induced by cancers or in chronic diseases, they may still provide an important novel target for therapy particularly if given in combination with suppressors of cytokine function.

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