Increased PD-L1 expression may be associated with the cytokine storm and $CD8^+$ T-cell exhaustion in severe COVID-19

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Severe Covid-19 is characterised by both a cytokine storm and lymphopenia with reduced frequency of $CD4^+$ and $CD8^+$ T-cells [1]. $CD8^+$ cytotoxic T-lymphocyte cells play a key role in virus clearance, thereby decreasing viral replication and viral load [2]. Numerous clinical studies have characterized the changes of $CD8^+$ T-cells in mild and severe COVID-19 patients that expose the importance of $CD8^+$ T-cells in the progression of Covid-19. However, the mechanisms by which the changes in $CD8^+$ T-cells that ensue are not well elucidated. The study by Vitte et al found that increased PD-L1 in basophils, eosinophils, monocytes and NK cells in severe COVID-19 patients, particularly the expression of PD-L1 in basophils and eosinophils, were correlated with COVID-19 severity [3]. These findings could provide a plausible explanation for $CD8^+$ T-cell exhaustion in COVID-19. The cytokine storm may be responsible for increased PD-L1 expression, which leads to $CD8^+$ T-cell exhaustion. However, the study failed to identify the importance of lymphopenia in COVID-19 severity, probably due to small sample numbers (89% in severe cases vs 71% in mild cases, not statisticallysignificant). Similarly, the cytokine storm was also not well characterized and correlated with PD-L1 expression in severe COVID-19.

In severe COVID-19, blood levels of proinflammatory cytokines such as IL-6, IL-17 and TNF-alpha are significantly increased together with increased activity of macrophages and neutrophils [4]. These cytokines could be the cause for the increased expression of PD-L1 on the surfaces of immune cells in COVID-19. It is well known that PD-L1 expression is regulated by various signalling pathways which are activated by proinflammatory cytokines (Fig. 1)[5]. For example, IL-6 can activate the STAT3 signalling pathway, which in turn increases the expression of PD-L1[5]. TNF-alpha can activate PI3K/Akt and NF-kB signalling pathways that also upregulate PD-L1 expression. These cytokines may have a synergistic effect on the expression of PD-L1. The PD-L1/PD-1 axis is a major regulator of $CD8^+$ T-cell functionalities and survivability. PD-L1 binds to and activates PD-1, resulting in $CD8^+$ T-cell dysfunction and apoptosis [5].

Elucidaton of a cytokine storm/PD-L1/PD-1/CD8 T-cell exhaustion axis may have important therapeutic implications. Inhibition of proinflammatory cytokines and activated signalling pathways that increase expression of checkpoint molecules may also be effective for recovering $CD8^+$ T-cells (Fig. 1). A recent study has correlated pro-inflammatory cytokines with changes of $CD8^+$ T-cells in COVID-19 [6]. Furthermore, anti-IL-6 treatment of COVID-19 patients increased $CD8^+$ T-cell frequency and functionalities [7]. In addition, blockade of PD-L1/PD-1 could be an approach that recovers $CD8^+$ T-cell numbers and functionalities. Also, anti-inflammatory cytokines may be used to decrease the inflammatory status and recover $CD8^+$ T-cells. For example, IL-15 has been proposed for the treatment of COVID-19 [4]. IL-15 can increase $CD8^+$ T-cell functionalities, $CD8^+$ memory T-cells and "memory-like" naive $CD8^+$ T-cells [8, 9]. While additional studies are required to further understand the mechanisms of $CD8^+$ T-cell exhaustion, it is plausible that approaches that target pro-inflammatory cytokines, activated signals, PD-L1/PD-1 could significantly contribute to the recovery of the repertorie of $CD8^+$ T-cells in fulminant Covid-19 cases (Fig. 1).

Figure Legend

Fig. 1 Pro-inflammatory cytokines and PD-L1/PD-1 axis in severe COVID-19

Pro-inflammatory cytokines bind to their receptors on immune cells to produce positive signals, which increase expression of PD-L1. PD-L1 binds to PD-1 on $CD8^+$ T-cell to produce inhibitory signals, which block the function of $CD8^+$ T-cells to secret perforin and granzyme B as well as cause apoptosis of $CD8^+$ T-cells. Blockades of pro-inflammatory cytokines, activated signalling pathways and immune check point proteins could be therapeutic options. Abbreviations: PD-L1, programmed death ligand-1; PD-1, programmed cell death protein-1.

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Conflicts of interest

We declare that we have no conflicts of interest.

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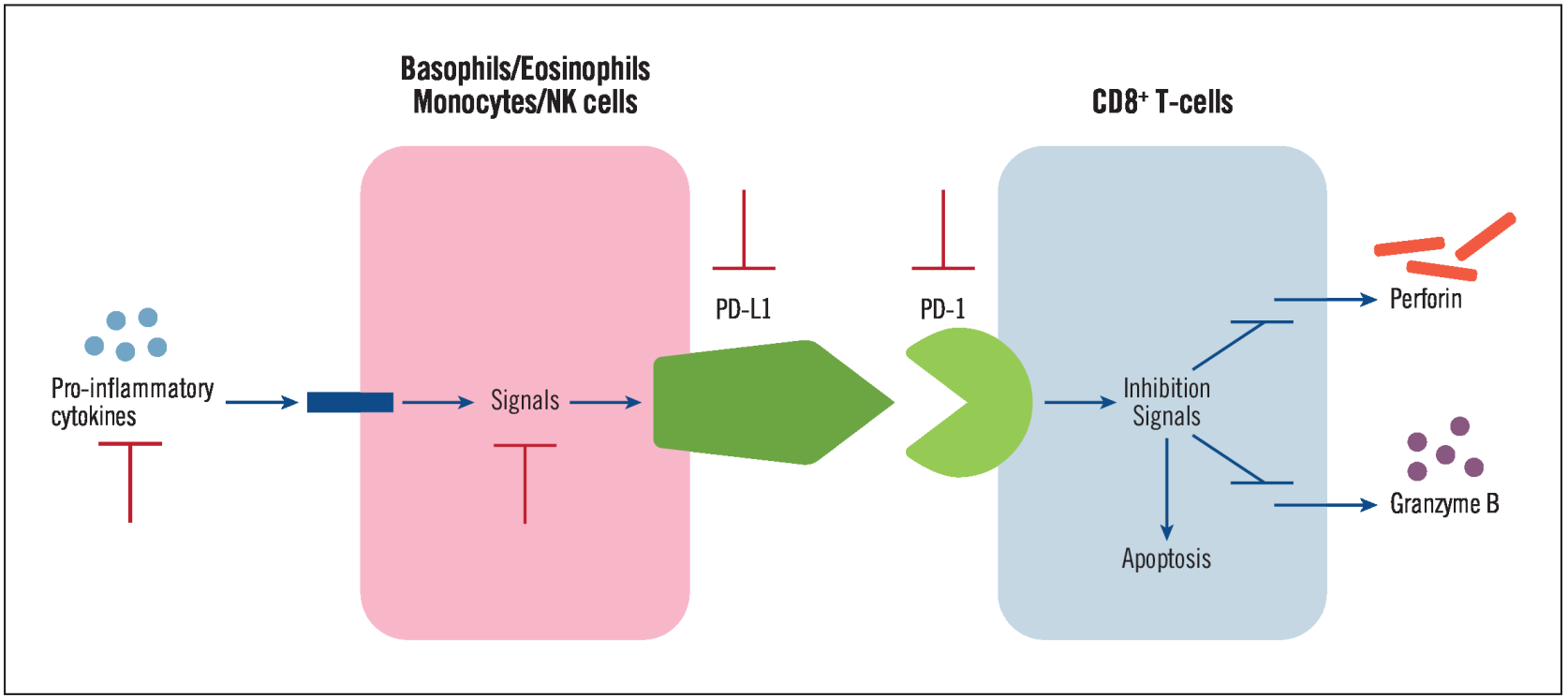
Figure 1


Basophils/Eosinophils
Monocytes/NK cells
CD8+ T-cells
Pro-inflammatory
cytokines
Signals
PD-L1
PD-1
Inhibition
Signals
Perforin
Granzyme B
Apoptosis