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COVID-19, Immune System and Hi-D FACS

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Editorial

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Editorial

In past we have used High-dimensional (Hi-D) immunophenotyping and Hi-D Fluorescein Activated Cell Sorting (Hi-D FACS) of peripheral blood to better study immune cells in health and viral disease [1-5]. Here we have reviewed the latest immunophenotyping studies in coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. This review sheds some light on relationship between disease severity and the host immune response on using Hi-D FACS.

Hi-D immunophenotyping of peripheral blood from COVID-19 patients revealed a significant shift in the ratio of immune cells, especially between mature and immature neutrophils associating with severity [6]. The disappearance of mature neutrophils and the increased numbers of immature neutrophils likely reflect gradual and sustained mobilization of these cells into the lungs in response to an ongoing inflammation, leading to premature release of immature neutrophils from the bone marrow [7]. A recent study, investigating several myeloid populations between circulating PBMCs and the lung lavage of COVID-19 patients showed that granulocytes represent the majority of total CD45+ lung infiltrates [8]. In addition, autopsies of COVID-19 fatalities showed typical lesions associated with toxic neutrophil effects [9,10]. Marked morphological abnormalities of the circulating neutrophils were reported in COVID-19 patients [11]. These cells present typical morphology of immature neutrophils and their precursors such as band shaped nuclei and a lower expression of CD16 and CD10 [12]. Immature neutrophil numbers strongly correlated with IL-6 and IP-10 during SARS-CoV-2 infection, IL-6 and IP-10 are consistently up regulated during a cytokine storm and are associated with severe ARDS [13-16].

Since IL-17 operates upstream of IL-1 and IL-6, and is a major orchestrator of sustained neutrophils mobilization it is reasonable that IL-17 could significantly affect the neutrophils compartment in COVID-19 patients. Also CD4 T-cells in COVID-19 patients are skewed towards a Th17 phenotype and increased CD4+CD161+ T-cells have been observed in recovered patients [6,17,18,]. These CD4+CD161+ T-cells are known to be either IL-17 producer cells or their precursors [19]. These studies indicate the re-circulation of these cells from the lung or secondary lymphoid organs after infection and support the possibility of IL-17 in mediating neutrophil damage to the lungs. Overall, this would support proposed anti-IL-17 or JAK2 inhibitor therapies for severe COVID-19 disease [20-22].

A marked decrease in T-cells has been observed, especially in subsets that possess cytolytic activity such as CD8, Vδ1 and Vδ2 T-cells [6]. Other studies have also shown a decrease of CD8+ during COVID-19 disease [18,23]. As for Vδ2 T-cells, which are not MHC-restricted T-cells [24,25], a general decrease in the periphery with disease severity has been shown [26]. Interestingly, γδ T-cells, in particular Vδ2, are known to participate in influenza immune response and actively recruit and activate neutrophils to the site of infection or inflammation [27,28].

Vδ2 T-cell counts in the periphery have been shown to decrease with ageing [29]. A systemic chronic low-grade inflammation, which was previously termed as inflamm-aging, has also been observed with higher basal levels of molecules such as CRP, TNF-a and IL-6 [30,31]. Age is a very well established risk factor for severe COVID-19 disease it has been postulated that the immature neutrophil to Vδ2 ratio takes into account the immunological age measured by Vδ2 T-cell counts of the patient which contributes to the improved sensitivity and specificity [6,32,33].

An early post illness onset of immature neutrophil-to-Vδ2 T-cell counts ratio (iNVD2R), using flow cytometer studies (of CD3; CD8; VD2; CD66b/CD15; CD16; CD10; CD45), has been suggested to be an excellent prognostic

screening tool for predicting probable patient progression to pneumonia or hypoxia (6).

In COVID-19 patients, CD8+ T cells and NKT cells lacking CD73 possess a significantly higher cytotoxic effector functionality compared to their CD73+ counterparts [34]. The decrease of CD73 on CD8+ T cells and NKT cells correlated with serum ferritin levels [34]. Lymphocyte CD73 expression in patients at different disease stages and its potential as prognostic markers or targets for immunomodulatory therapies.

Hi-D FACS has also confirmed absolute numbers of lymphocyte subsets were differentially decreased in COVID-19 patients according to clinical severity [35]. In severe disease (SD) patients, all lymphocyte subsets were reduced, whilst in mild disease (MD) NK, NKT and γδ T cells were at the level of healthy controls (HC) [35]. Follow up samples revealed a marked increase in effector T cells and memory subsets in convalescing but not in non-convalescing patients. These data suggest that activation and expansion of innate and adaptive lymphocytes play a major role in COVID-19. Additionally, recovery is associated with formation of T cell memory as suggested by the missing formation of effector and central memory T cells in SD but not in MD [35].

Hi-D FACS analysis of immune cells including NK cell counts showed significantly higher in patients with COVID-19, also effector memory CD8+ T-cell counts significantly increased during a convalescent period of 1 week, TIM-3+ Tfh-like cell and CD226+ Tfh-like cell counts significantly increased and decreased, respectively, during the same period. The high expression of NK cells is important in innate immune response against SARS-CoV-2, and the increase in effector memory CD8+ T-cell counts, the up-regulation of inhibitory molecules and the down-regulation of active molecules on CD4+ T cells and Tfh-like cells in patients with COVID-19 would benefit the maintenance of balanced cellular and humoral immune responses, may prevent the development of severe cases and contribute to the recovery of patients with COVID-19 [36].

Using Hi-D FACS for understanding immune responses in the context of clinical severity is foundation to overcome the lack of effective anti-viral immune response in severely affected COVID-19 patients and can offer prognostic value as biomarker for disease outcome and control.

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