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Review

Hallmarks of immune response in COVID-19: Exploring dysregulation and exhaustion

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ABSTRACT

One and half year following the occurrence of COVID-19 pandemic, significant efforts from laboratories all over the world generated a huge amount of data describing the prototypical features of immunity in the course of SARS-CoV-2 infection. In this Review, we rationalize and organize the main observations, trying to define a "core" signature of immunity in COVID-19. We identified six hallmarks describing the main alterations occurring in the early infection phase and in the course of the disease, which predispose to severe illness. The six hallmarks are dysregulated type I IFN activity, hyperinflammation, lymphopenia, lymphocyte impairment, dysregulated myeloid response, and heterogeneous adaptive immunity to SARS-CoV-2. Dysregulation and exhaustion came out as the trait d'union, connecting abnormalities affecting both innate and adaptive immunity, humoral and cellular responses.

1. Introduction

"*After all, do not fear difficult times. The best comes from there.*" - Rita Levi Montalcini

The COVID-19 pandemic has dramatically revealed the impact of emerging infections in the 21st century world. Less than a year after SARS-CoV-2 isolation, vaccines have been developed using new platforms and administered on a large scale. Globally, as of October 2021, there have been more than 236 million confirmed cases of COVID-19, including more than 4 million deaths, and more than 6 billion vaccine doses have been administered [1]. Innate and adaptive immune responses are essential in protection against viral infections and in successful vaccination. We present a comprehensive overview of the main characteristics of immune response in different phases of COVID-19.

Taking inspiration from the classification of the major properties of cancer [2], we tried to identify the hallmarks defining the immune response in COVID-19 (Fig. 1). Indeed, we know that SARS-CoV-2 infection can profoundly affect the functionality of the immune system, leading to profound dysregulation and immune cell exhaustion. We identified six hallmarks that collectively define the major immunological abnormalities in COVID-19. The first hallmark, occurring early after the infection, is the dysregulated type I IFN response, which blunts the establishment of an efficacious rapid antiviral response. The inability to restrict viral replication promotes the production of high levels of pro-inflammatory cytokines, favoring the occurrence of systemic hyper-inflammation (second hallmark). Cytokine storm is accompanied by a dramatic lymphocyte depletion (third hallmark) in both blood and secondary lymphoid organs. We now know that lymphocytes are not only affected in terms of absolute numbers, but also from a functional point of view. Indeed, lymphocyte impairment (fourth hallmark) is another typical feature of severe COVID-19. Myeloid cell response dysregulation also occurs (fifth hallmark), affecting all cell subsets. The sixth hallmark concerns SARS-CoV-2 specific adaptive immune response that is highly heterogeneous in terms of magnitude, with a strong correlation with clinical outcome.

2. Dysregulated type I IFN activity

Following SARS-CoV-2 infection in the upper respiratory tract, type I IFN release is a major mechanism involved in limiting viral replication [3]. Accordingly, type I IFN is highly effective also on SARS-CoV-2 replication, as demonstrated by *in vitro* experiments that showed its suppressive ability when exogenously administered [4]. In addition, type I IFN promotes the development of effective innate and adaptive immune responses. Indeed, it favors maturation of antigen presenting cells, activation of NK cells and both $CD4^+$ and $CD8^+$ T cell responses [5]. Given the pivotal role of type I IFN pathway in the antiviral

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response, viruses have evolved to counteract or delay the production of this cytokine. SARS-CoV-2 does not make an exception, and it has been shown that non-structural proteins (nsp) 1 and nsp6 are particularly effective in suppressing type I IFN response [6]. Furthermore, ORF3b and ORF6 are also potent antagonists of interferon activity [7,8]. In agreement with this, severe COVID-19 patients are characterized by an impaired type I IFN response, with no IFN-β and low IFN-α production [9,10]. However, other studies reported instead an increased type I IFN signature in severe patients, with high expression of IFN-stimulated genes (ISG) in bronchoalveolar lavage fluid cells [11] and circulating monocytes [12]. In agreement, single-cell RNA sequencing (scRNAseq) data showed that PBMNC from moderate COVID-19 patients had an inflammatory signature driven by TNF-α and IL-1, while in severe patients type I IFN response was also present [13]. The differences observed in human studies may be related to different time of sampling. Indeed, the importance of an appropriate early response is confirmed by *in vivo* murine studies showing that delayed type I IFN production orchestrates an inappropriate proinflammatory response with lung immunopathology in the context of SARS-CoV-1 infection [14]. On the contrary, early administration of type I IFN in this model has a protective effect with reduced viral load and controlled inflammation [14]. Additional studies obtained in mice demonstrated a role for type I IFN in the recruitment of proinflammatory cells into the lungs, thus contributing to pathology [15]. Other mouse models of viral infections have shown that impaired type I IFN response is associated with increased pathology due to the concomitant production of high levels of proinflammatory cytokines [16]. Supporting this concept, a genetic study has shown that loss of function variants affecting type I IFN response are significantly enriched in patients with life threatening SARS-CoV-2 pneumonia [17]. The same group also reported the presence of autoantibodies neutralizing type I IFN, predisposing to the development of severe COVID-19 [18]. Altogether, the data suggest that viral-mediated delayed production of type I IFN is the first step towards COVID-19 worsening.

3. Hyperinflammation

Some patients with COVID-19 develop a hyperinflammatory syndrome that is characterized by elevations in proinflammatory markers and multiorgan failure resembling the cytokine release syndrome that may complicate chimeric antigen receptor (CAR)-T cell therapy [19–21, 23–25]. Cytokine release syndrome is a systemic inflammatory response that can be triggered by various therapies, infections, cancers, autoimmune diseases, and monogenic disorders [26,35]. Active evaluation of efficacy and safety of immunomodulatory therapies in COVID-19 patients through extensive approaches integrating clinical, laboratory, pathologic, and imaging features has played a crucial role in the management of COVID-19 [27,28]. Nonetheless, case-series, clinical trials enrolling small numbers of patients, and observational cohort studies are not sufficient for good clinical practice and suffer from potential biases. Large randomized clinical trials are necessary to improve patients' outcomes and provide reliable data to guide evidence-based clinical decisions [29].

Recovery from viral infections requires an effective host immune response that eliminates the virus, or at least controls viral replication. Basically, the effector activity of the immune response is counterbalanced by mechanisms of suppression and/or regulation. Sustained viral replication resulting from impaired type I IFN-γ production and persistent activation of the immune response result in a continuous inflammatory process whose consequences are detrimental [30]. A dysregulated response is indeed ineffective in clearing the virus and causes epithelial and endothelial damage, vascular leakage, up to organ failure [31–33]. SARS-CoV-2 infection recapitulates the critical role of an effective immune response and the devastating effects of immune dysregulation. After an initial response with generally mild to moderate symptoms, some patients show a progression to an excessive and dysregulated inflammatory response [34] (Fig. 2). This is a hyperinflammatory response that equals a "cytokine storm", a potentially life-threatening systemic inflammatory syndrome involving elevated plasma cytokine levels and immune-cell hyperactivation with consequent acute systemic inflammatory symptoms and organ dysfunction [35].

A complex, interconnected network of innate and adaptive cell types, signaling pathways, and cytokines is involved in COVID-19 associated cytokine storm. Inflammatory markers (C-reactive protein, serum amyloid A, fibrinogen, ferritin) are highly increased and correspond to elevated serum cytokine levels including IL-1β, IL-1RA, IL-2, IL-4, IL-6, IL-7, IL-10, IL-19, G-CSF, TNF-α, IFN-γ, but also chemokine levels including monocyte chemoattractant protein (MCP)-1 (CCL2), MCP-2 (CCL8), MCP-3 (CCL7), CCL3, CXCL8 (IL-8), CXCL9, CXCL10 (IP-10), CXCL5 [25,36–38,40–44,46,47]. Circulating levels of IL-6 are significantly higher in severe disease than mild to moderate disease and predict COVID-19 severity and survival [49–51]. It is yet unknown the exact pathophysiology underlying COVID-19 associated cytokine storm. Immune hyperactivation could result from inappropriate triggering or danger sensing, impaired magnitude of response (either inappropriate or

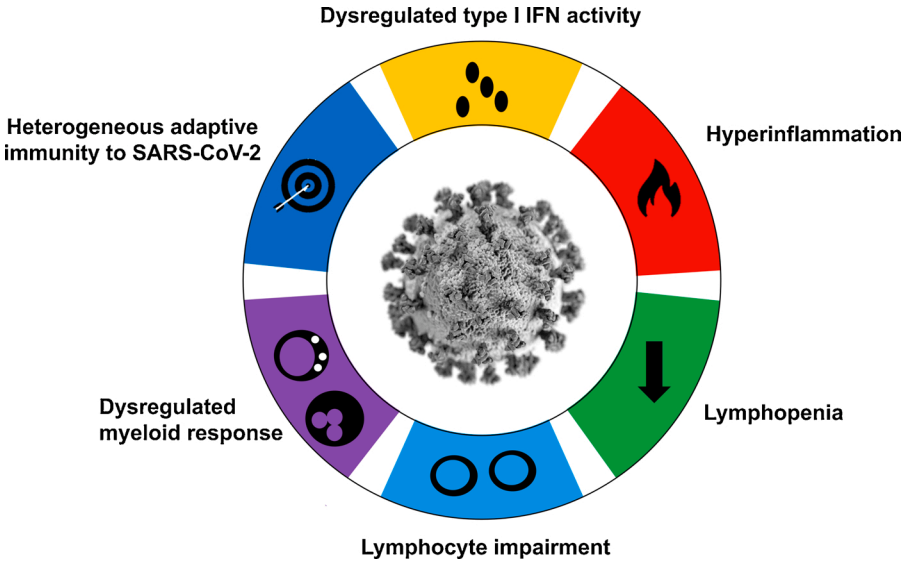

Fig. 1. The Hallmarks of immune response in COVID-19.
In severe COVID-19 patients, six main immunological abnormalities can be observed. 1) Dysregulated type I IFN activity occurs early after the infection, impairing viral replication control. 2) The unrestrained viral replication promotes the production of high levels of pro-inflammatory cytokines (hyperinflammation). 3) Cytokine storm is commonly accompanied by decreased absolute numbers of circulating lymphocytes (lymphopenia). 4) Lymphocytes display also functional impairment in terms of cytokine production, cytotoxic activity and exhibit increased expression of exhaustion markers. 5) Myeloid cell response is also affected, with profound alterations towards an immature and hyperactivated phenotype. 6) Heterogeneous cellular and humoral adaptive immune response to SARS-CoV-2 associates to severe disease. [SARS-CoV-2 ultrastructure is reproduced from Public Health Image Library (PHIL ID #23312)]

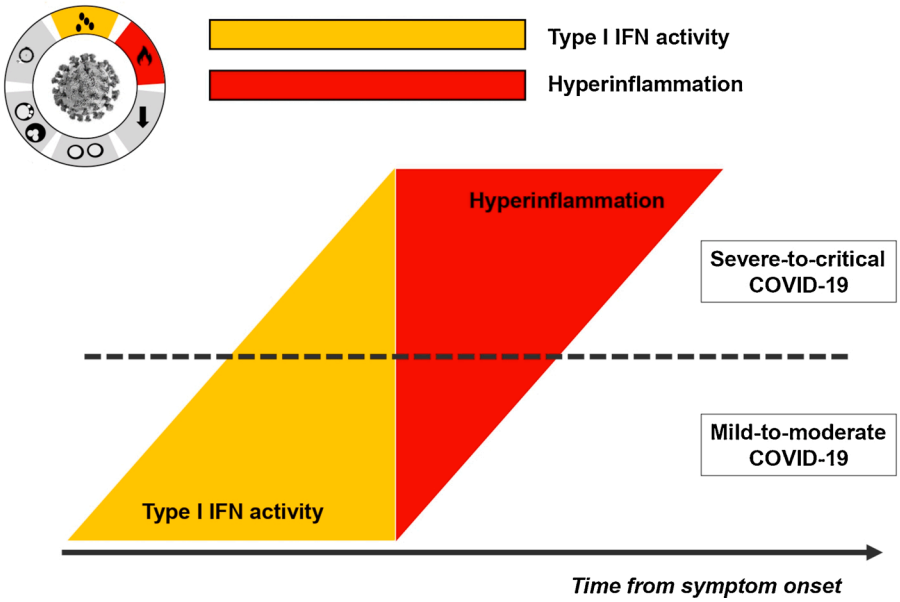

Fig. 2. Dysregulated type I IFN activity and hyperinflammation.
In the early phases of mild-moderate COVID-19, an efficacious type I IFN response restrains viral propagation, allowing proper control of the infection with the activation of a balanced immune response and moderate production of pro-inflammatory cytokines. However, in some patients several mechanisms can impair the early type IFN activity, including viral evasion systems, the presence of anti-IFN autoantibodies or genetic predisposition with mutations of molecules involved in IFN-signaling pathway. In any case, the delayed and reduced activity of type I IFN response cannot control viral replication, which leads to the compensatory, aberrant production of pro-inflammatory cytokines. This is the basis of cytokine storm occurring in severe COVID-19 patients.

ineffective), and/or failure to resolve inflammation because of ongoing viral replication or immune dysregulation [35,52]. Multisystem inflammatory syndrome in children (MIS-C) is a rare but serious complication of COVID-19 in the pediatric population; MIS-C is a hyperinflammatory syndrome with delayed presentation, generally occurring 2–6 weeks after SARS-CoV-2 infection [53–56]. In MIS-C associated cytokine storm, cytokines as IL-7, IL-8 and IFN-γ have been described to play a crucial role, differently from what is observed in adults with severe acute COVID-19 disease [47,57,58].

Many monoclonal antibodies targeting pro-inflammatory cytokines involved in COVID-19 cytokine storm have been used as immunomodulators to dampen the hyperinflammation. On March 2020, tocilizumab, a humanized anti-IL-6 receptor monoclonal antibody, approved in 2017 for the treatment of CAR-T cell-induced cytokine storm and used in many rheumatologic diseases, was proposed as immunomodulatory therapy in patients with severe COVID-19 [59–61]. However, studies on the efficacy of tocilizumab in patients with COVID-19 have been controversial, particularly considering differently enrolled populations and study designs [62–65,67–70,245]. IL-6 levels have been correlated with SARS-CoV-2 viral load, disease severity, and prognosis [49,50,71]. Blocking the IL-6 axis might account for improved pulmonary vascular perfusion: vascular radiologic score and alveolar-arterial oxygen gradient significantly improved after tocilizumab administration [68]. Among hospitalized adults with progressive severe or critical COVID-19 who have elevated markers of systemic inflammation, tocilizumab is suggested in addition to standard of care rather than standard of care alone [67]. It has been shown that in COVID-19 patients circulating IL-6 levels inversely and significantly correlate with granzyme-A producing NK cells [49]. In fact, increased levels of IL-6 inhibit NK cytotoxicity and downregulate the expression of perforin and granzyme [72–75]. Remarkably, in a small cohort of COVID-19 patients requiring intensive care, tocilizumab resulted in restoring of the cytotoxic potential of NK cells, as well as in reversion of metabolic alterations [49,76]. Sarilumab a monoclonal antibody with higher affinity for the IL-6 receptor than tocilizumab has been used in severe-critical COVID-19 patients showing conflicting results [64,77–79]. Anakinra, a recombinant human IL-1 receptor antagonist, approved for use in several autoinflammatory syndromes, has been studied for the treatment of severe COVID-19 with promising results [80–82,251,258]; however, no evidence of clinical benefit was observed in adults hospitalized with COVID-19 mild-moderate pneumonia [83]. Canakinumab, a human anti-IL-1β monoclonal antibody has been proposed in COVID-19 treatment, but efficacy needs to be fully demonostrated [84–86]. In the context of COVID-19-associated cytokine storm, targeting the JAK-STAT signaling pathway via JAK-inhibitors has emerged as a possible key in controlling the downstream signal mediated by cytokine receptors [87,88]. Ruxolitinib (JAK1/JAK2 inhibitor), baricitinib (JAK1/JAK2 inhibitor) and tofacitinib (pan-JAK1 inhibitor) have been used in COVID-19 hospitalized patients with good results [42,89–91,243]. In a randomized clinical trial, tofacitinib was superior to placebo in reducing the incidence of death or respiratory failure through day 28 [91]. Combination treatment of baricitinib plus remdesivir resulted superior to remdesivir alone in reducing recovery time and accelerating improvement in clinical status among patients with COVID-19, particularly among those receiving high-flow oxygen or noninvasive ventilation [92,93]. In hospitalized adults with severe COVID-19 and increased inflammatory markers but not on invasive mechanical ventilation, baricitinib rather than no baricitinib is recommended [67]. Evaluation of safety profile of JAK-inhibitors in COVID-19 must be addressed [94,95].

In 2003 in a correspondence to the NEJM Sung and Lee explained the rationale of the use of corticosteroids in SARS: “we used corticosteroid treatment to suppress the cytokine storm, hoping that would stop the progression of pulmonary disease. And, in fact, in many cases, it did. Lung shadows started to resolve and oxygenation improved after corticosteroid treatment. We must emphasize that corticosteroids were not used to treat acute respiratory distress syndrome (ARDS)” [96]. Immunosuppressive treatment had already been a major point for discussion in SARS-CoV infection [97–101]. Given the hyperinflammatory state associated with COVID-19, immunomodulatory treatments have been evaluated and are under evaluation in the management of patients with COVID-19. In hospitalized patients, the use of dexamethasone for up to 10 days resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone but not among those receiving no respiratory support [102]. In a prospective meta-analysis of clinical trials of critically ill patients with COVID-19, administration of systemic corticosteroids (dexamethasone, hydrocortisone, or methylprednisolone), compared with usual care or placebo, was associated with lower 28-day mortality, even if there are clinical trials showing conflicting results [45,103–105]. To date the use of corticosteroids in COVID-19 is recommended only in critical cases, suggested in hospitalized patients with severe disease, while discouraged in mild-moderate disease not requiring supplemental oxygen; no indications are available for those patients with mild-moderate COVID-19 in the outpatient setting [67,240]. In a cohort of children and

adolescents with suspected MIS-C, no evidence was found that recovery from disease differed after primary treatment with intravenous immunoglobulins (IVIG) alone, IVIG plus corticosteroids, or corticosteroids alone [106]. Restricting the analyses to those children who met the WHO criteria for MIS-C, a modest evidence of benefit for recovery with corticosteroids alone compared to IVIG alone was observed [106]. Another study demonstrated that among children and adolescents with MIS-C, initial treatment with IVIG plus corticosteroids was associated with a lower risk of new or persistent cardiovascular dysfunction compared to IVIG alone [107]. These data support the rapid initiation of immunomodulatory therapy in patients with MIS-C, as it can be life-saving [108].

In conclusion, more studies focusing on the mechanisms of hyper-inflammation in COVID-19 are necessary to support the use of immunomodulatory therapies, particularly in different subsets of patients and at different times of disease course.

4. Lymphopenia

A common laboratory feature of SARS-CoV-2 infection is lymphopenia (i.e. an absolute lymphocyte count < 1000 cell/μl). Patients with COVID-19 show significant decrease of absolute numbers of circulating T cells (T $CD3^+$, T $CD4^+$, T $CD8^+$), B cells ($CD19^+$), NK cells ($CD56^+$), and NKT cells ($CD3^+CD56^+$) [38,49,109,111,113]. The CD4/CD8 ratio is generally higher than 1.5, as a result of a greater reduction of $CD8^+$ T cells than $CD4^+$ T cells [49,249] (Fig. 3). Loss of the NKT cell subset has been reported as one of the prominent features of COVID-19, which became apparent already within the first week of hospital admission and could predict disease evolution [114]. On the contrary, no significant alterations were described in peripheral blood [49,116] for T follicular helper cells (Tfh). Data on T regulatory cells are highly heterogeneous, with some reports showing an increase while some others showing a decrease in the circulation of severe COVID-19 patients [117,118]. Lymphopenia occurring in severe COVID-19 affects also the B cell compartment. A marked reduction in B cell absolute numbers has been described [49,177], although the percentages of total and naïve B cells did not show differences between patients and healthy controls [49,119]. Lymphopenia is not limited to circulating cells, indeed it also occurs in secondary lymphoid organs: lymphocyte depletion of spleen and of lymph nodes has been observed in autoptic studies, similarly to SARS infection [120–123]. In the spleen, atrophy of the white pulp with even complete loss in some fatal cases has been described, while the red pulp appears to be congested and hemorrhagic [121,124]. In lethal COVID-19 cases, lymph nodes from the cervical, mediastinal and hilar regions revealed moderate-severe capillary stasis and edema, proliferation of extrafollicular plasmablasts (particularly, IgG^+ and IgM^+ plasmablasts), mild-moderate plasmacytosis, predominance of $CD8^+$ T cells, sinus histiocytosis with hemophagocytosis [125,246]. Moreover, lymph nodes and spleen are characterized by hypoplasia or absence of germinal centers with decreased follicular dendritic cells and Tfh cells, as well as striking reduction in Bcl-6^+ germinal center B cells paralleled by loss of circulating transitional and follicular B cells [126,246]. Tfh reduction in secondary lymphoid organs has been associated with severe inflammation, indeed high TNF-α levels were detected inside and outside follicles [126]. The increased presence of extrafollicular plasmablasts in the absence of follicular hyperplasia suggests rapid or primarily transient B cell immune response bypassing the germinal center response [127,128,246]. The negative correlation between the presence of secondary follicles and SARS-CoV-2 viral load in the lungs might be consistent with delayed germinal center response [246]. It is known that most patients with sepsis develop signs of profound and long-term immunosuppression either concomitantly with initial inflammation or delayed [129–134]. Mechanisms contributing to sepsis-induced immunosuppression include cellular apoptosis, autophagy, endotoxin tolerance, metabolic and transcriptional reprogramming [129,135]. Sepsis induces a tolerogenic state that contributes to immunosuppression and explains the increased susceptibility to secondary infections after a severe primary infection [136]. Severe-critical COVID-19 has similarities with sepsis [134,137,138] and immunosuppression is indeed a pathological feature [94,95,139]. Starting with the first descriptions of COVID-19 case-series in 2019 at the beginning of the pandemic, a correlation between disease severity and lymphopenia had readily been demonstrated. Severe COVID-19 patients requiring intensive care have indeed significantly lower absolute number of circulating lymphocytes compared to patients with moderate disease [22,140–143,145,146] (Fig. 3). Lymphopenia on admission has then been correlated with poor outcomes in COVID-19 patients [147,148,247]. Lower lymphocyte count is associated with increased mortality, acute respiratory distress syndrome, need for intensive care, and severe disease, particularly in younger patients [247]. During hospitalization, lymphocytes count is more reduced in

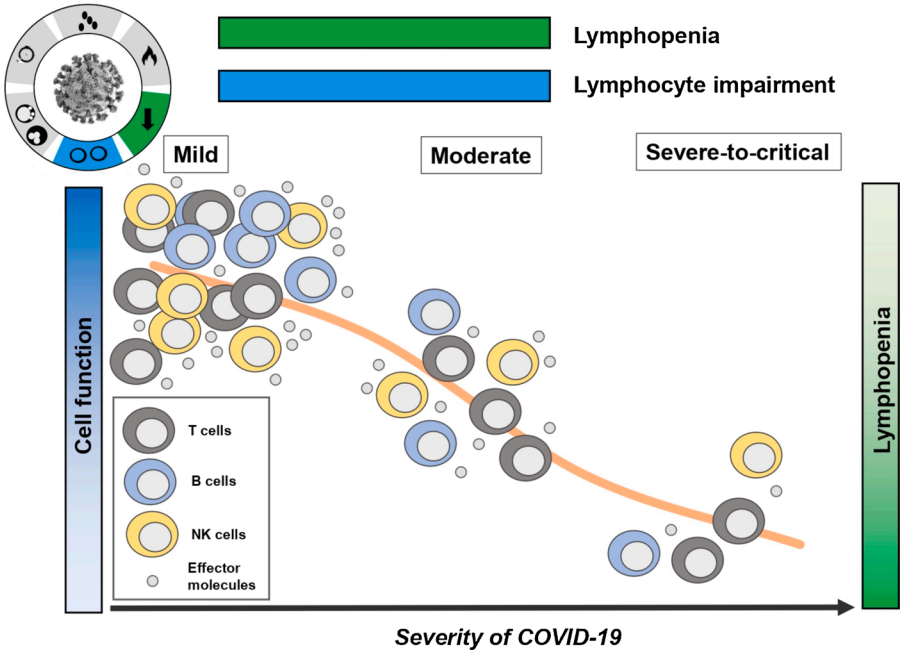

Fig. 3. Lymphopenia and lymphocyte impairment. COVID-19 progression towards severe phase is characterized by marked reduction of circulating lymphocytes. This defect affects all lymphocyte subsets i.e., T cells, B cells, NK cells. Lymphocyte absolute numbers are decreased also in secondary lymphoid organs, as demonstrated by post-mortem studies. Lymphocytes are profoundly affected in terms of functionality, as they are characterized by reduced production of pro-inflammatory cytokines and cytotoxic potential. Accordingly, lymphopenia and lymphocyte function impairment positively correlate with disease severity and all lymphocyte subsets display an exhausted phenotype.

patients who do not survive and have a more severe disease compared to patients who recover or have milder disease [22,149]. In survivors there is, indeed, a progressive increase of lymphocyte counts over time [22]. Lymphopenia is generally lower 4–7 days after symptoms onset and is concomitant with increase of pro-inflammatory cytokines [150,151]. It should be noted that other respiratory viral infections are associated with transient lymphopenia, from influenza to SARS [152–155]. It was initially speculated that peripheral lymphopenia in patients with COVID-19 could be a consequence of local recruitment into the lung tissue or lymphocyte adhesion to the endothelium [156,242]. Autopsy lung specimens have shown interstitial and perivascular lymphocytic infiltration of varying extent [157,158]. However, in severe-critical COVID-19, lymphopenia could be a consequence of elevated levels of IL-6, IL-10 and TNF-α through a direct effect on T cell subsets, but also as an indirect effect on dendritic cells and neutrophils [38,110]. In addition, hyper-activated T cells or elevated expression of pro-apoptotic molecules such as FAS (CD95), TRAIL (TNF-related apoptosis-inducing ligand) or caspase 3 could also contribute to lymphocyte reduction [38,116,159]. Increased levels of circulating apoptotic T cells, defined by expression of cleaved caspase-3 and/or cleaved PARP, were indeed observed in COVID-19 patients [161]. Various mechanisms have been hypothesized as implicated in the occurrence of lymphopenia in COVID-19, nonetheless no definite pathogenesis has been described yet [162]. Longitudinal analyses of TCR and BCR repertoire in COVID-19 patients could reveal important findings on the causes and effects of lymphocyte depletion [163–165].

5. Lymphocyte impairment

Another hallmark that characterizes the lymphocyte compartment in COVID-19 is the altered functionality. We know indeed that both innate and adaptive lymphocytes are significantly impaired in severe SARS-CoV-2 infection, as a result of delayed type I IFN production, consequent cytokine storm and viral clearance inability. Although a direct relationship between these parameters and lymphocyte exhaustion has not been proved yet, we may speculate that persistent severe inflammation may impact on lymphocyte functionality. Indeed, it has been proved that inflammation and oxidative stress may impact main T cell effector functions and differentiation [166]. In addition, it has been demonstrated that increased levels of both soluble and membrane-bound PD-L1 positively correlate with COVID-19 severity [167,241,250]. This may result in increased ligation of cognate PD-1 receptors on lymphocytes thus resulting in their impaired functionality. Herein we describe the major abnormalities observed in both innate and adaptive lymphocytes (Fig. 3).

5.1. NK cells

NK cells have a primary role in viral clearance and, accordingly, it has been described their accumulation in the lungs of COVID-19 patients [144,168]. However, alterations in NK cell response have been reported in COVID-19 patients, especially in those with severe disease [114]. NK cells display reduced IFN-γ and TNF-α production, together with reduced expression of cytotoxic molecules such as granzymes and perforin [49,169–174]. These alterations are particularly evident in patients requiring intensive care therapy. Impaired NK cell functionality is directly dependent on the hyperinflammation occurring at later stages of COVID-19. Indeed, granzyme A expression inversely correlated with IL-6 serum levels [49]. Targeting IL-6 signaling with tocilizumab restored granzyme expression in a cohort of critically ill patients, while the JAK-STAT inhibitor ruxolitinib increased TNF-α production [42,49]. NK cells from SARS-CoV-2 infected subjects not only show reduced expression of cytotoxic molecules, but also reduced degranulation as assessed by CD107 expression when tested ex vivo [170–173]. In agreement with the reduced NK cell functionality, these cells exhibited an increased expression of inhibitory checkpoint molecules such as PD1, TIGIT and Tim-3 [173,175]. Supporting these data, scRNAseq showed that $CD56^{dim}$ NK cells, classically considered cytotoxic cells, are primarily depleted in severe COVID-19 patients, while $CD56^{bright}$ NK cells, known to produce high levels of IFN-γ and TNF-α, are depleted in all COVID-19 patients [12]. Single cell transcriptome data further reinforced the idea that NK cells in COVID-19 express inhibitory receptors as PD1, LAG-3 and Tim-3 [12]. A selective expansion of "adaptive" $NKG2C^+$ $CD57^+$ NK cells has been demonstrated in COVID-19. This NK cell subset is commonly associated with CMV infection [176], but it can also expand during other viral infections in CMV seropositive subjects. Of note, adaptive NK cell expansion was primarily demonstrated in CMV-seropositive severe COVID-19 patients, but in absence of an ongoing anti-CMV immune response [175]. This finding suggests that the expansion of $NKG2C^+$ $CD57^+$ NK cells may be directly induced by SARS-CoV-2 infection. Additional studies are needed to clarify the role of this cell subset in COVID-19.

5.2. T cells

T cell compartment is significantly affected in severe SARS-CoV-2 infection. Phenotypic analysis demonstrated that $CD4^+$ T cells from COVID-19 patients do not show alterations in the frequency of naïve and effector/central memory populations. Instead, $CD8^+$ T cells display a marked reduction in the frequency of naïve cells, with a parallel expansion of terminally differentiated $CCR7^-CD45RA^+$ TEMRA cells [49,119]. High expression of the surface marker CD57 further suggests the increased senescence of $CD8^+$ T cells in COVID-19 [49,119]. Furthermore, $CD8^+$ TEMRA cells from COVID-19 patients show a reduced proliferative capacity [119]. Additional studies have also demonstrated the upregulation of inhibitory checkpoints by both $CD4^+$ and $CD8^+$ T cells in COVID-19 patients, especially in the "non-naïve" compartment [114,116,119,159,171]. Of note, PD1 expression by $CD4^+$ T cells significantly increased during the first 5 days post hospital admission, but then it normalized in moderate patients while remaining elevated in severe ones [114]. In agreement with the increased expression of exhaustion markers, both $CD4^+$ and $CD8^+$ T cells from COVID-19 patients showed a significantly reduced production of pro-inflammatory cytokines when restimulated ex vivo [38,49]. Moreover, an altered cytotoxic capacity has been proposed for $CD8^+$ T cells from severe patients [174]. Although characterized by reduced functionality, both $CD4^+$ and $CD8^+$ T cells showed increased expression of HLA-DR and CD38, markers of cell activation, and of Ki-67, marker of T cell proliferation [116,119,178], and these parameters correlated to disease severity [178,114]. Unconventional T cells, including γδ T, mucosa-associated invariant T and invariant NKT cells in the peripheral blood of COVID-19 patients showed increased PD1 expression and, in agreement with their exhausted phenotype, produced less IFN-γ than cells from healthy donors [179].

Analysis of bronchoalveolar lavage (BAL) samples from COVID-19 patients demonstrated an enrichment of both $CD4^+$ and $CD8^+$ T cells in lungs [180] exhibiting clonal expansion [181]. Increased PD1 expression was observed in T cells from BAL than PB [182]. Two subsets of Th17 cells have been detected in COVID-19 BAL samples, one exhibiting a tissue-residency phenotype and characterized by GM-CSF production [181]. Of note, this subset shared clones with Th1 cells [181], suggesting that Th17 cells undergo inflammation-driven polarization into Th1 at sites of infection [183]. $CD8^+$ T cells were less represented in BAL of severe patients than in patients with moderate infection [144] suggesting an important role for these cells in SARS-CoV-2 eradication.

5.3. B cells

Regarding memory B cells, it was reported an increase in the $CD21^-$ $CD27^-$ population in moderate and severe COVID-19 patients. This subset represents exhausted B cells, characterized by reduced

proliferative capacity and its expansion has been already described in other viral infections [184–186]. Moreover, plasmablasts are significantly expanded in severe COVID-19 subjects [159,177,178] and show high Ki-67 expression [178]. Plasmablasts from severe COVID-19 patients display also a profound oligoclonal expansion [178] and reduced expression of genes involved in glycolysis, when compared to asymptomatic individuals [188]. Similarly to T cells, also B cells from severe patients show upregulation of apoptosis-related genes [174], thus providing a rationale for their reduction. Transcriptome data show that B cell activation pathways are more suppressed in severe than in moderate patients, suggesting a dysfunctional response that may limit the activity of these cells [174]. In agreement, another report showed that B cell transcriptomes in asymptomatic individuals have traits of increased type I IFN response, increased NF-kB signaling and increased BCR triggering [188].

6. Dysregulated myeloid response

Accumulating evidence has shown that the myeloid compartment is significantly affected in severe COVID-19 patients (Fig. 4).

6.1. Dendritic cells

Dendritic cells (DC) are a heterogeneous population of antigen presenting cells (APC), commonly divided in CD123^{+} plasmacytoid DC and conventional (myeloid) DC [189]. Conventional DC can be additionally distinguished in CD141^{+} cDC1 and CD1c^{+} cDC2 [189]. Collectively, DC are crucial players in priming CD4^{+} and CD8^{+} T cells responses. In addition, pDC are a primary source of type I IFN following viral infections. All DC subsets are markedly reduced in the circulation of COVID-19 subjects when compared to healthy donors [159,189–191]. Interestingly, while pDC and cDC1 are reduced in all SARS-CoV-2 infected subjects irrespective of disease severity, cDC2 deficiency is more pronounced in critically ill patients [191]. In agreement, an enrichment of cDC2 in the lungs of severe COVID-19 patients was demonstrated [191]. This observation suggests that the loss of pDC and cDC1 is not caused by tissue redistribution. In agreement, increased expression of pro-apoptotic genes has been demonstrated in pDC from COVID-19 patients [192], suggesting that cell death may be a cause for the reduced absolute numbers. pDC also demonstrated functional impairment, with reduced expression of viral sensors TLR7 and DHX36 [192]. Accordingly, pDC from COVID-19 subjects demonstrated impaired IFNα production [193]. Moreover, pDCs from severe patients showed a reduced expression of genes related to IFN signaling, while increased activation of pathways related to TNF-α, IL-6 and NfKb [192]. This observation suggests that the suppression of type I IFN response in severe patients leads to the compensatory production of high levels of proinflammatory cytokines. The same imbalance was observed also in cDC subsets, together with a functional impairment also in cDC2 which exhibited decreased activity of several transcription factors [192]. SARS-CoV-2 cannot productively infect dendritic cells *in vitro* but can activate these cells to express costimulatory molecules and produce high IFNα levels [194]. This finding suggests the possibility that the reduced absolute numbers and functionality of circulating pDC observed in COVID-19 patients are not the result of a direct cytopathic viral effect, rather the result of systemic hyperinflammation occurring in severe COVID-19.

6.2. Monocytes

Monocytes are a subset of large mononuclear cells, historically considered an intermediate subset between bone marrow precursors and tissue macrophages. Monocytes have a crucial role in inflammation and pathogen fighting. Three subsets of circulating monocytes can be defined in humans: CD14^{++} CD16^{-} classical, CD14^{++} CD16^{+} intermediate and CD14^{+} CD16^{++} non-classical monocytes. Classical and intermediate monocytes are recruited at sites of infection or injury and can differentiate in macrophages or monocyte-derived dendritic cells. These monocyte subsets produce high levels of TNF-α, nitric oxide and reactive oxygen species (ROS), fundamental components of an efficient pathogen-fighting activity. Non-classical monocytes instead have a patrolling activity but are also involved in antiviral activity [195]. The three monocyte subsets are present in the blood in precise ratios, however significant changes can occur during infections [196]. Although the absolute number of circulating monocytes is not different in COVID-19 patients from that in healthy subjects [189], profound alterations in monocytes' phenotype and functionality have been described. Indeed, the percentage of non-classical monocytes is markedly reduced in the circulation of COVID-19 patients, particularly those requiring intensive care therapies, with a parallel increase in the frequency of classical monocytes [189,191,197]. The redistribution of monocyte subsets in the circulation is paralleled by an accumulation of non-classical monocytes

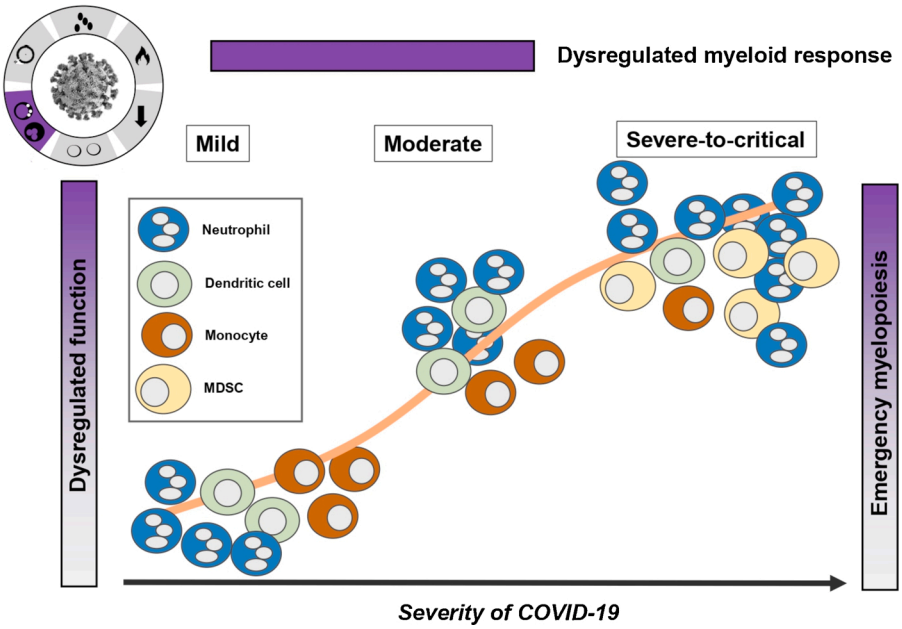

Fig. 4. Dysregulated myeloid response.
COVID-19 progression towards the severe phase is characterized by quantitative and qualitative alterations in the myeloid cell compartment. Immature cells appear in the circulation, as a sign of inflammation-driven emergency myelopoiesis. Neutrophils accumulate in severe COVID-19 but display an aberrant production of NETs, expression of activation markers and PD-L1. Monocytes show altered composition, with depletion of the non-classical subset from the circulation, and functionality, with increased production of pro-inflammatory cytokines and reduced surface expression of HLA-DR. DC are significantly depleted in severe patients and produce low IFN-α levels. Severe COVID-19 is characterized also by the appearance of myeloid derived suppressor cells (MDSC) with immune suppressive properties.

in the lungs, suggesting a selective recruitment of this population at site of inflammation [191]. Monocytes in COVID-19 patients also display altered phenotypic and functional properties. Indeed, these cells display significantly reduced levels of HLA-DR expression and an aberrant increase in activation markers such as CD64, CD11b and CD163 [189,198]. These phenotypic alterations are influenced by systemic inflammation, given that CRP levels are negatively correlated with HLA-DR expression [189,191]. In agreement, *in vitro* administration of the anti-IL-6R mAb tocilizumab restored monocyte HLA-DR expression [199], while *in vivo* suppression of cytokine signaling with JAK-STAT inhibitor ruxolitinib led to a normalization of activation markers expression [42]. Monocytes in COVID-19 patients also display an altered functionality, with increased TNF-α and IFN-γ but reduced IL-1β production, and an altered expression of cyclooxygenase 2 (COX-2), a rate-limiting enzyme in prostaglandin production [190]. Moreover, monocytes from COVID-19 patients display an impaired metabolism, with defective oxidative phosphorylation, glycolysis and oxidative burst [187], suggesting bioenergetics alterations in late stage disease. Dynamic alterations in the myeloid compartment have been described in the course of COVID-19, with the presence of HLA-DR^{hi}CD11c^{hi}/HLA-DR^{hi}CD83^{hi} monocytes with a strong antiviral IFN-signature in mild patients, substituted by the occurrence of HLA-DR^{low} monocytes in the severe phase of the disease [200].

The profound alteration of circulating monocytes can be the result of inflammation-driven emergency myelopoiesis, with an increased myeloid output from the bone marrow to fight the viral infection [201]. High expression of the proliferation marker Ki67 by circulating monocytes has been correlated to emergency myelopoiesis in other viral infections [202]. In agreement, monocytes from severe COVID-19 patients displayed high Ki67 expression, which correlated to levels of systemic inflammation [190]. Circulating monocytes in COVID-19 subjects also express high levels of the chemokine receptor CCR2, while its cognate chemokine is highly produced in the airways, suggesting a route for monocyte recruitment in the respiratory tract.

6.3. Neutrophils

Circulating neutrophils display quantitative and qualitative alterations in the course of SARS-CoV-2 infection. Although the absolute number of total white blood cells is generally normal in severe COVID-19, the leukocyte composition is profoundly affected. Indeed, the marked reduction of circulating lymphocytes is paralleled by a significant increase in the neutrophil count. Increased neutrophil to lymphocyte ratio is thus a typical feature of severe COVID-19 [49,178]. The composition of neutrophil subset is also heterogeneous, with the appearance of immature cells due to inflammation-driven myelopoiesis that can be related to high G-CSF levels in the plasma of critical patients [200,203]. Neutrophils from severe COVID-19 patients downregulate CD62 L expression while increasing the expression of CD64 and CD274 (PD-L1), as a sign of activation, dysfunction and immunosuppression [200]. In addition, neutrophils in severe COVID-19 are characterized by the hyper-expression of the activation marker CD66b [189]. In agreement, a transcriptional signature suggesting neutrophil hyper-activation has been correlated to critical illness, and neutrophil activation status on the day of hospitalization can predict the transfer to the intensive care unit [204,203]. From a functional point of view, phagocytosis capacity does not differ in mild versus severe COVID-19 patients, although a significantly reduced production of ROS was demonstrated in the latter group [200]. Neutrophil extracellular traps (NETs) production is also dysregulated in COVID-19. NETs are extracellular fibers made of DNA assembled with histones and granule-derived enzymes such as myeloperoxidase, with both anti-microbial and tissue destroying activities. Increased levels of NETs were reported in the plasma of COVID-19 patients and correlated with disease severity [205]. Post-mortem studies revealed NETs accumulation also in the lungs of patients who died from SARS-CoV-2 infection [206]. SARS-CoV-2 can infect neutrophils and activate NETs release, which in turn promote lung epithelial cell death, thus contributing to COVID-19 pathology [206].

6.4. Myeloid derived suppressor cells

Myeloid derived suppressor cells (MDSC) are a subset of bone-marrow derived, immature innate cells that increase in the circulation in cancer, inflammatory diseases, or infections [207,208]. Two subsets can be typically distinguished, monocytic (M-MDSC) or neutrophilic (PMN-MDSC), both involved in the suppression of innate and adaptive immune responses, with the contemporary promotion of regulatory cell development [208]. PMN-MDSC are typically enriched in the low-density neutrophil (LDN) fraction and suppress immune cells mainly via the release of ROS and arginase I. M-MDSC instead act mainly via iNOS and arginase I. Other immune suppressive mechanisms have also been described, including the release of IL-10, TGF-β and the enzyme IDO1. Increased levels of circulating MDSC in severe COVID-19 are a sign of immune dysregulation. Both subsets of MDSC are particularly increased in patients requiring intensive care, and their frequency correlates with proinflammatory cytokines in the serum [200,209,210]. PMN-MDSC from COVID-19 patients suppress T cell response and IFN-γ production through iNOS and TGF-β mediated mechanisms [209], while M-MDSC were found to suppress T cell response in an arginase I-mediated mechanism [211]. Given their immunosuppressive properties and their accumulation in severely ill patients, MDSC can contribute to the immune dysregulation that occurs at late stages of COVID-19 [210]. LDNs show intermediate levels of CD16 expression and their levels directly correlate with parameters of inflammation. Moreover, LDNs are highly enriched in the bronchoalveolar lavage fluid of COVID-19 patients [212]. LDNs have a pro-inflammatory gene signature, display enhanced NETs formation and interact with platelets, thus promoting the blood hypercoagulability that is typical of COVID-19 [212].

7. Heterogeneous adaptive immune response to SARS-CoV-2

Antigen-specific immune response against viruses is essential both at first encounter with pathogens for successful control of the infection, and in the long-term by development of immune memory and prevention of re-infection. The identification of antigen-specific T cells, B cells and antibodies against SARS-CoV-2 antigens represents an important tool to monitor the features of adaptive immune response in the course of acute COVID-19, in the recovery phase and months/years after infection. Seminal works published in the last year have demonstrated that a specific adaptive immune response occurs following SARS-CoV-2 infection [213–216]. Data on humoral response in COVID-19 patients are predominant, because the evaluation of serum levels of SARS-CoV-2-specific antibodies is easier and more rapid than the identification of antigen-specific circulating T cells. However, it was reported a significant direct correlation between the frequency of SARS-CoV-2 specific CD4$^+$, CD8$^+$ T cells and the levels of virus-specific antibodies [48,252,253], suggesting a coordinated activity of all branches of adaptive immunity. SARS-CoV-2 infection induces a wide spectrum of clinical manifestations ranging from no symptoms to pauci-, mild- or severe symptoms culminating in ARDS and multi-organ failure up to death. Many authors reported that the entity of SARS-CoV-2-specific immune response, both humoral and cell-mediated is lower in the asymptomatic patients than in the symptomatic ones [48,255,256]. However, T cells from asymptomatic individuals produced higher levels of IFN-γ and IL-2, while those from symptomatic subjects secreted more proinflammatory cytokines TNF-α, IL-1β and IL-6 [218]. In addition, people with severe COVID-19 displayed a dysregulated adaptive immunity to the virus, with altered CD4$^+$ and CD8$^+$ T cell responses and, in some cases, delayed or absent production of neutralizing antibodies [252] (Fig. 5). Higher disease severity occurring in aged individuals is associated to scarcity of naïve CD4$^+$ and CD8$^+$ T cells, thus confirming that a limited repertoire of naïve lymphocytes impairs the

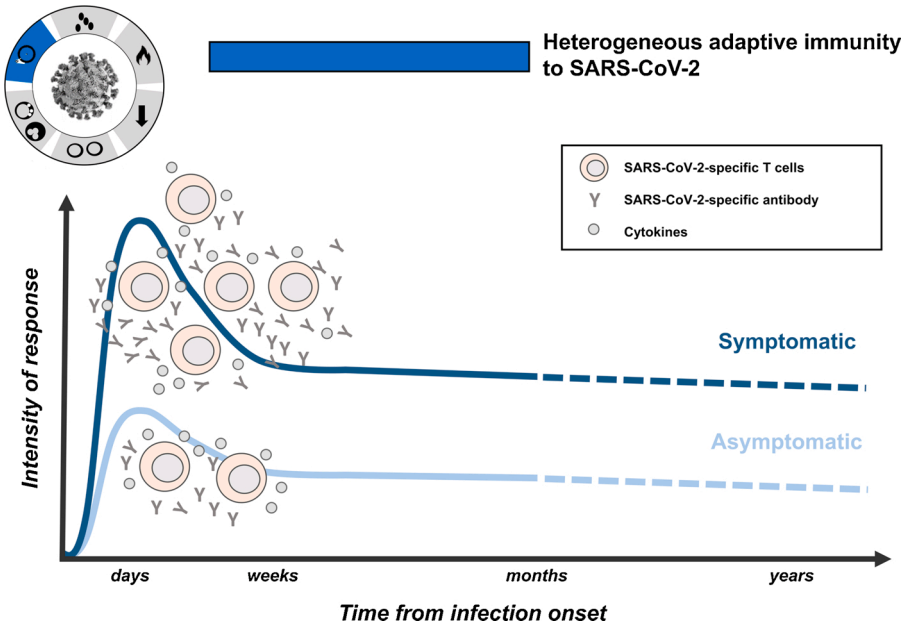

Fig. 5. Heterogeneous adaptive immunity to SARS-CoV-2.
In asymptomatic individuals, rapid activation of adaptive immunity to SARS-CoV-2 allows to rapidly control the infection, with limited production of virus-specific antibodies and T cells. T cells are functionally superior, in asymptomatic than symptomatic patients, with higher production of pro-inflammatory cytokines. Continuous lines represent the observed trend of SARS-CoV-2 specific immune response in symptomatic and asymptomatic individuals, whereas the dotted lines are hypothetical long-term memory immune responses.

capacity to mount a rapid and effective antiviral response [252]. These findings are in agreement with the observation that rapid induction of SARS-CoV-2-specific T cells associates with mild disease, while delayed response occurs in critically ill patients [219]. Altogether, these data suggest that a more severe disease is a consequence of a dysregulated priming of anti-SARS-CoV-2-specific immunity, which leads to a hyperactive and uncoordinated response. Moreover, SARS-CoV-2-specific T cell responses are lower in children when compared to adults [221]. This heterogeneity could also be due to the presence of pre-existing cross-reactive antigen-specific T cells or antibodies in SARS-CoV-2 unexposed individuals [213,216,222]. In addition to the frequency, the deep phenotypic characterization of antigen-specific T cells is critical to understand their specific function, such as the kind of cytokine production and the expression of activation/inhibition markers. It has been reported that SARS-CoV-2-reactive T cells are polyfunctional due to the production of more than one effector cytokine (IL-2, IFN-γ and TNF-α) and highly express immune-checkpoints PD-1 and TIGIT [48] as sign of their recent stimulation. Interestingly, both these features are more evident in symptomatic than asymptomatic patients. Prolonged T cells activation due to disease and virus persistence can induce T cells exhaustion as supported by high level of TIGIT, PD-1 and Tim-3 on $CD4^+$ and $CD8^+$ T cells, despite their TCR specificity, correlating with disease severity [113,223,224]. Moreover, PD-L1 is upregulated in SARS-CoV-2 infected cells and in COVID-19 patients' lung biopsies and increased serum levels of soluble PD-L1 are considered a negative prognostic marker [250]. One of the most frequent questions at the moment is how long will the antigen-specific immune response be maintained, which is fundamental to guarantee long-lasting protection. During the last year, several reports have been accumulated demonstrating the persistence of SARS-CoV-2-specific immune response, both humoral and cell-mediated, at different time points after recovery from natural infection [225–228,234].

The kinetics of development and maintenance of immunological memory against SARS-CoV-2 shows that specific memory B cells arise over 3–5 months reaching a plateau phase at 6–8 months, supporting the long-lasting antibody production in that period. On the other hand, SARS-CoV-2-specific $CD4^+$ and $CD8^+$ memory T cells peak within the first month and then slowly decline in the following months [220,225]. In addition, it has been described the development of SARS-CoV-2-specific stem cell like memory T cells regardless of disease severity [229]. Similar findings were reported also for humoral specific immune response, since the gradual decrease of total SARS-CoV-2 Ig levels was associated with a high neutralising antibody titres and a robust specific memory B cell response in both moderate and severe COVID-19 recovered patients, irrespective of disease severity at hospitalisation [254]. Although the majority of previously infected individuals maintain high levels of circulating specific $CD4^+$ T cells and antibodies, about 10–20 % of recovered subjects showed a borderline specific adaptive immune response, suggesting they could be more susceptible to reinfection and thus may benefit from vaccination [225,227,234]. All these data indicate that the balance between functionality and dysregulation of the components of the specific immune response (B cells, T cells and antibodies) determine the effective anti-SARS-CoV-2 protection over time. Of note, for future investigation on the functional features and on the durability of SARS-CoV-2-specific adaptive immune response it is important to note that longitudinal evaluation of persistence of infection-induced Spike-specific immunity will be influenced by vaccination. Moreover, it should be considered that additional SARS-CoV-2 antigens, different from the "classic" Spike, Nucleoprotein and Membrane may be of importance to track SARS-CoV-2-specific memory durability. This is further supported by the recent identification of antibodies against non-structural/accessory proteins in COVID-19 patients, as well as of HLA-I peptides derived from both canonical open reading frames (ORFs) and internal out-of-frame ORFs of S and N proteins [217,230]. These data open the way to further investigation and strategic approach in monitoring SARS-CoV-2 specific immune response.

Since the publication of SARS-CoV-2 genome sequence at the beginning of 2020, the scientific community has produced an unprecedented effort to develop efficacious vaccines against COVID-19. Given the central role of Spike in the infectious process, this protein has become the main target for vaccine development. Different platforms have been approached, but those that entered earlier in clinical trials are based on mRNA or non-replicating viral vectors. mRNA vaccines from Pfizer-BioNTech (BNT162b2) and Moderna (mRNA-1273) are now currently used in Europe and the USA; viral-vector based vaccines from AstraZeneca and Janssen are both used in Europe, while only Janssen in the USA. Ad26.COV2.S from Janssen is the only vaccine that requires one shot, while the others are being administered with a two doses schedule. All vaccines displayed good immunogenicity, eliciting both humoral and cellular immune responses [231,232]. In particular, it has been shown that the second dose administration can significantly boost

the levels of specific neutralizing antibodies, T cells and B cells [233, 238]. The second dose is also important to increase the levels of $CD4^+$ T cells and antibodies with neutralizing activity against SARS-CoV-2 variants of concern [235,259]. Given the efficacy and the safety profiles of currently approved vaccines, in most countries they have been offered to the whole population, regardless of prior SARS-CoV-2 infection. However, it should be noted that none of the currently approved vaccines has been tested in clinical trials in people who recovered from COVID-19. Emerging data have demonstrated that one vaccine administration is sufficient to achieve high levels of anti-Spike immunity in people with a past SARS-CoV-2 infection. Indeed, it has been shown that following the first dose of mRNA vaccine, COVID-19 recovered subjects display high levels of anti-Spike IgG, including those with neutralizing activity [233,236,237]. Moreover, in recovered COVID-19 subjects the first vaccine dose maximizes the levels of circulating, Spike-specific, T and B cells [233,238]. On the contrary, the administration of the second vaccine dose in ex−COVID-19 individuals is associated with a contraction of neutralizing antibody levels, as well as Spike-specific T and B cell frequencies [233,239]. Thus, the second scheduled inoculation seems detrimental, rather than beneficial, in this population, suggesting that over-boosting Spike-specific immunity may lead to anergy and exhaustion. This hypothesis should be seriously taken into consideration and tested. Evaluation of exhaustion markers expressed by Spike-specific $CD4^+$ T cells in naïve and COVID-19 recovered subjects following the complete vaccination cycle did not show differences among the two groups [233]. However, it should be noted that functional assays requiring cell stimulation *in vitro* might not allow the identification of exhausted T cells, given that these cells may not be activated following antigenic stimulation. Thus, additional studies using different experimental approaches are needed to understand if the second vaccine dose in COVID-19 recovered subjects is associated with immune cell exhaustion.

8. Conclusion and future perspectives

The six hallmarks presented in this Review summarize the main features of the immune response in the course of COVID-19. SARS-CoV-2 infection represents a major challenge for the immune system, and the deriving immune response has a significant impact on the patient's outcome. A balanced, well-coordinated and early-established response involving both innate and adaptive immunity can promote a rapid eradication of viral infection, with minimal symptoms. On the contrary, a late-occurring and uncoordinated response opens the way towards disease worsening, promoting abnormalities that affect all compartments of the immune system and that reinforce each other in a positive feedback loop. Immune dysregulation is the causative event for the organ dysfunction that occurs in late-stage disease, thus representing an important target for therapeutic intervention. For this reason, further deepening the knowledge of the complex mechanisms controlling immune dysfunction in COVID-19 will be crucial to design appropriate interventions.

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Declaration of Competing Interest

None.

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