Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review Article

Exhaustion and over-activation of immune cells in COVID-19: Challenges and therapeutic opportunities

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ABSTRACT

Exhaustion of immune cells in COVID-19 remains a serious concern for infection management and therapeutic interventions. As reported, immune cells such as T effector cells (Teff), T regulatory cells (Tregs), natural killer cells (NKs), and antigen-presenting cells (APCs) exhibit uncontrolled functions in COVID-19. Unfortunately, the mechanisms that orchestrate immune cell functionality and virus interaction are still unknown. Recent studies linked adaptive immune cell exhaustion to underlying epigenetic mechanisms that regulate the epigenetic transcription of inhibitory immune checkpoint receptors (ICs). Further to that, the over-activation of T cells accompanied by the dysfunctionality of DCs and Tregs may enhance uncontrollable alveoli inflammation and cytokine storm in COVID-19. This might explain the reasons behind the failure of DC-based vaccines in inducing sufficient anti-viral responses. This review explains the processes behind the over-activation and exhaustion of innate and adaptive immune cells in COVID-19, which may contribute to developing novel immune intervention strategies.

1. Introduction

SARS-CoV-2 is the virus causing COVID-19, which beget the new world corona pandemic. COVID-19 displayed distinct patterns of cellular and humoral immune disorders compared to previous corona infections. It induces exhaustion of T cells, DCs, and NKs in the early and mild stages, but over-activation dramatically increases in severe cases, resulting in a cytokine storm that was linked to the risk of dyspnea and death. Early reports concluded that in COVID-19, macrophages act as the first antigen-presenting cell (APC) responder to viral invasion, eliciting innate and adaptive immune responses [1,2]. It generates macrophage inflammatory protein 1 (MIP1) and type I interferons (IFNs), which activate T cell responses [3,4]. In addition, macrophages produce interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-), and interleukin-1 beta (IL-1β) [5]. In response to macrophage alarming and Macrophage-T cell interaction, T cell subset differentiation occurs quickly, resulting in the proliferation of T helper 1 (Th1), cytotoxic T cells (CTLs), and Th17. Recent research has revealed that macrophage hyperactivation in COVID-19 causes acute respiratory distress syndrome (ARDS) and dyspnea [6]. This is characterized primarily by an increase in the number of $FNC1^+$ macrophages in bronchoalveolar lavage fluid (BALF). Hyperactive macrophages secrete high levels of proinflammatory cytokines such as IFN, induced protein 10 (IP10), IL-6, IL-17, TNF-α, TGF-β, and IL-10/23 after activation, resulting in cytokine storm syndrome [7]. Further, activation of T cell subsets immediately releases high levels of IFN-γ, IFN-α/β, monocyte chemotactic protein 1 (MCP1), IL-21, and other proinflammatory cytokines [1,3]. High inflammatory cytokines stimulate NK cells and effector T cells to infiltrate the alveoli, which leads to an increase in the destruction of infected epithelial cells.

Unfortunately, the interaction between responded immune cells in the alveoli remains unclear. Early studies found that upregulation of inhibitory immune checkpoints (ICs) in COVID-19 is linked to exhaustion of T cells and NK cells [8]. The exhaustion of $CD8^+$ T cells is evident in mild/moderate infections but it seems to be lower in severe infections that showed an increase in the cytokine-producing T cells [8]. Analyzing ICs on T cells of a cohort of 108 patients with mild, moderate, and severe COVID-19 showed upregulation of *CTLA-4*, *PD-1*, *CD39*, *CD160*, *TIM-3*, *VISTA*, *2B4*, *TIGIT*, *NKG2A*, and *Gal-9* [9]. Importantly, some scientists questioned the expression of ICs in $CD8^+$ T cells in COVID-19 and the link to the exhaustion phenomenon, claiming that T cells that recognize SARS-CoV-2 peptide pools (M/N/S) have higher frequencies of cytokine-

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producing T cells even when they express ICs [9]. Another study revealed that in the early convalescent phase, multimer^{+} cells showed early developed effector-memory characteristics. In the late convalescent period, the frequency of stem-like memory cells rose among multimer^{+} cells. The percentage of interferon-producing cells was much lower among SARS-CoV-2-specific CD8^{+} T cells than among those specific to the influenza A virus. They concluded that SARS-CoV-2-specific CD8^{+} T cells are not exhausted but functional [10]. As a result, they propose that the expression of ICs in CD8^{+} T cells has no significant impact on the exhaustion in SARS-CoV-2, except for lowering the expression of IFN-γ. However, in COVID-19 and other chronic infections, a link between persistent exhaustion of CD8^{+} T cells and epigenetic changes in ICs transcription has been experimentally demonstrated [11,12]. Furthermore, ICs blockade, like PD-1 and NKG2A, enhances significant CD8^{+} T cell immune responses in chronic infections [13,14]. Ex vivo blockade of PD-1 in exhausted T cells isolated from COVID-19 patients restored T cell functional response to COVID-19 [15]. Furthermore, PD-1/PD-L1 blockade improves the symptoms of cancer patients infected with COVID-19, who had complete virus clearance based on a nasopharyngeal swab test [16]. Overall, the link between ICs overexpression and exhaustion in CD8^{+} T cells have been reported in several studies. Releasing low levels of cytokines is not strong evidence to dismiss the link between ICs and CD8^{+} T cell exhaustion. Therefore, more clinical trials targeting ICs in CD8^{+} T cells could be effective in the enhancement of COVID-19 immunotherapy. Furthermore, a deep understanding of immune modulation supporting virus infectivity is strongly needed to realize how can we prevent severe complications of COVID-19.

2. Immunomodulation and COVID-19 progression

Most COVID-19 patients showed lymphopenia, the elevation of C-Reactive Protein (CRP), serum ferritin, and procalcitonin levels. Patients with COVID-19 show low percentages of basophils, eosinophils, and

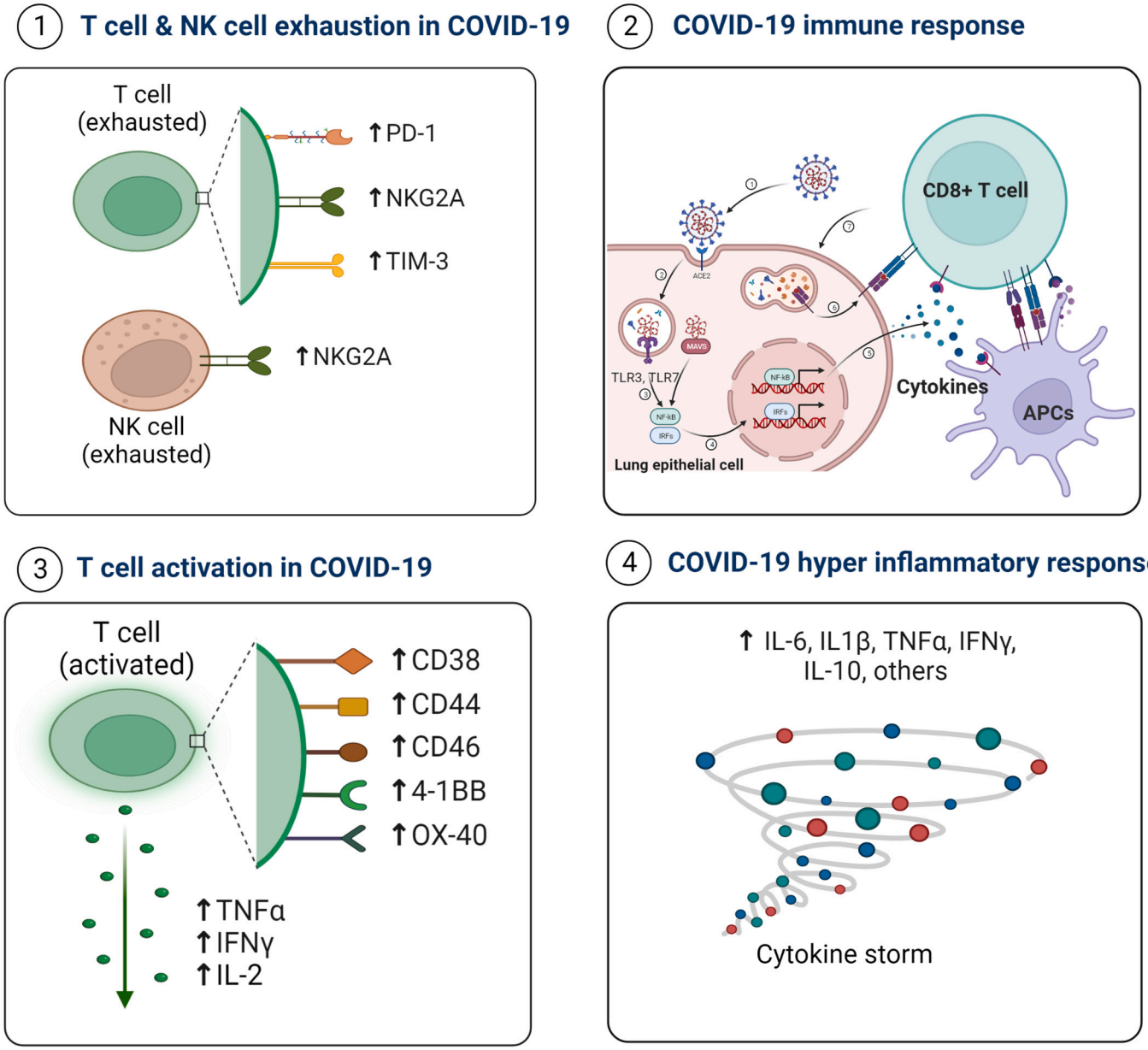

Fig. 1. Schematic diagram shows potential scenarios of immune interaction with SARS-CoV-2. 1) immune cells express different inhibitory ICs on exhausted T and NK cells; 2) immune response when SARS-CoV-2 invades epithelial cells starts with antigen presentation and cytokine release; 3) in the severe phase of COVID-19, T cells over-activation leads to the release of many types of inflammatory cytokines and surface markers; 4) hyper inflammation induce cytokine storm.

monocytes, while the number of neutrophils increases. In severe cases, the neutrophil/lymphocyte ratio (NLR) was higher than in mild cases [17]. NLR has been shown to be a predictor of pneumonia and a clear marker of systemic inflammation and infection [18]. Many studies have revealed that an increase in NLR indicates the development of severe COVID-19 infections and a serious disruption in homeostasis [19]. Nonetheless, recent reports have shown that purified human neutrophil defensin (HNP1–3) cannot inhibit SARS-CoV infectivity [20]. It is unclear whether the increase in neutrophils is related to lymphocyte exhaustion. The exhaustion of cytotoxic T cells and NK cells are a distinct feature of COVID-19 cases [10,21–23]. Despite the fact that $CD8^+$ T cells and NK cells share many effector characteristics, activation processes, and immune suppression effects, the primary function of NK cells is distinct [24]. On the other hand, differentially expressed genes (DEGs) of COVID-19 T cells revealed that the downregulated DEGs involved T-cell activation, signaling pathways mediated by cytokines, and Th17 cell differentiation [25]. Furthermore, recent reports suggest that SARS-CoV-2 mediates immune modulation to enhance immune cell exhaustion and over-activation at different stages of COVID-19 pathogenesis, as presented in Fig. 1.

As several studies stated, SARS-CoV-2 induces a strong release of cytokines in a life-threatening manner that can be described as systemic hyper inflammation and immune dysregulation. It is well known that COVID-19 increases the levels of several pro-inflammatory cytokines/chemokines such as IL-6, MCP1, IL-21, IL-1β, CCL2, CXCL10, and IFN-γ [26]. Once SARS-CoV-2 invades epithelial cells, the activation of innate inflammatory cells starts strongly and keeps working with high trends that alleviate responses of functional adaptive immune cells. It's thought that activation of NF-Kβ elicits the expression of IRF4, COX2, and other signals that enhances the expression of ICs leading to suppression of adaptive immune cells response [27]. However, up to date, it is not known how SARS-CoV-2 orchestrates type of immune responses. We think that the high frequency of viral invasion induces the activation of multiple antigen-presenting cell types such as macrophages and DCs that elicit antigen persistence expression. Antigen persistence induces ICs transcription and overexpression on adaptive immune cells such as $CD4^+$ T cells, $CD8^+$ T cells, and B cells, hence inducing adaptive immune cell exhaustion [28–30]. Besides, exhaustion of some other immune cells such as DCs and NK cells is still unclear in COVID-19.

2.1. SARS-CoV-2 mediates innate and adaptive immune cell modulation

As known, the innate immune system recognizes viral RNAs, including SARS-CoV-2, via pattern recognition receptors (PRRs) such as NOD-like receptors (NLRs), RIG-I-like receptors (RLRs), and Toll-like receptors (TLRs), which induce the release of interferons (IFNs) and the activation of macrophages, NK cells, and $CD8^+$ T cells [31–34]. PRR activation via the NF/IRF7 and MAPKs pathways results in the activation of inflammatory cytokines [35]. Based on data from animal model studies, plasmacytoid dendritic cells (pDCs) serve as the primary APCs, releasing high levels of type I interferons that regulate responses to SARS-CoV infections [36]. In pDCs, TLR7/TLR9 recognizes the viral nucleic acid and induces type I IFNs, which promote the release of inflammatory cytokines via activation of NF-κB and IRF7 [37]. At moderate infections of COVID-19, monocyte-derived $FCN1^+$ macrophages and not fatty acid binding protein 4 ($FABP4^+$) alveolar macrophages were observed as predominant APCs [38]. Furthermore, pDCs were considered high in severe COVID-19 infections, and high levels of type I IFNs was linked to an increased number of pDCs [39]. However, some studies have found that severe COVID-19 impairs pDC function, resulting in increased viral infectivity [40]. Previous studies have suggested that pDCs are the most important subsets for recognizing virally-infected cells and releasing anti-viral IFNs [41]. Recently, Andreas Wack reported that pDCs, conventional dendritic cells (cDCs), and monocytes become exhausted in severe COVID-19 infections due to increased apoptosis-inducing pathways, when compared to moderate COVID-19 infections [42].

A study conducted in the United Kingdom reported that $CD68^+NP^+$ macrophages and monocytes were highly accumulated in the kidneys of COVID-19 patients due to acute kidney tubular damage [7]. scRNA-seq analysis of peripheral blood mononuclear cells and immunostaining of post-mortem tissue revealed that macrophages express the ACE2 receptor and contain SARS-CoV-2 nucleoprotein (NP) [43,44]. However, it is not clear whether the virus infects macrophages, or the NP positivity reflects the activity of macrophage uptake which remains unknown, but these phenomena presented that virus exhibits special mechanisms to modulate immune cell responses. According to previous research, macrophages, and myeloid dendritic cells (mDCs) both play an important role in the over-activation of adaptive immune cells in severe COVID-19 by releasing high levels of IL-6 in the alveolar space, resulting in a fulminant and fatal hypercytokinaemia. Thus, there is a different behavior for DCs and macrophage subsets at different stages of COVID-19, indicating that SARS-CoV-2 mediates some epigenetic modulation of immune cell functions, which is still unclear.

As known, differentiation of naïve $CD4^+$ T cells into memory subsets and effectors is one of the most fundamental facets of T-cell-mediated immunity [45]. The balance between memory and naïve $CD4^+$ T cells is critical for immune maintenance. In moderate cases of COVID-19, memory cell subsets decrease while naïve $CD4^+$ T cells increase [21]. A high memory: naïve ratio indicates the onset of T cell dysfunction [17]. The molecular mechanism by which SARS-CoV-2 mediates immune imbalance and T cell impairment are still unknown. Furthermore, the relationship between immune checkpoints (ICs) overexpression and virus interaction leading to exhaustion remains to be elaborated. Scientists suggest a change in the epigenome of immune cells, which regulates the complete transcription program leading to uncontrollable transcription of ICs [46]. The global epigenome may have changed because of the high load of SARS-CoV-2. Although over-activation of inflammatory responses in severe COVID-19 was linked to the decrease and dysfunctionality of T regulatory cells (Tregs) [47], the role of Tregs is still controversial. According to several studies, moderate and severe COVID-19 showed a relative increase in immunosuppressive Tregs [48,49]. The increase of Tregs is due to the high release of inflammatory mediators. In contrast, some studies reported that the number of Tregs was decreased in severe COVID-19 patients [50,51]. Single-cell screening in severe infections revealed that the expression of FOXP3 was significantly lower than moderate, but CD25 expression was significantly higher [52]. The reason was attributed to increasing in furin protease, which facilitates viral particle entrance [52]. Further reports on COVID-19 patients observed that Tregs present perturbations expression due to IL-6 and IL-18 that may individually contribute different facets of these COVID-19–linked perturbations [53]. These results indicate that the mechanism by which SARS-CoV-2 mediates immunomodulation is still unclear, as well as the timing of suitable immunotherapy intervention remains to be elucidated.

2.2. NK exhaustion in SARS-CoV-2 infection

NK cells are a type of innate immune cells that recognize virally infected cells and promote death fate [54]. The increase of NK cells attributes to acute viral infections. NK cells induce cytokine-producing $CD8^+$ T cells and sustained T cell responses, which may prevent the exhaustion of $CD8^+$ T cells. During early chronic infections, $CD49a^-CD49b^+NKp46^+$ NK cell subsets increase and show low expression of Ly49 and TRAIL, but CD94/NKG2A and KLRG1 expressions increase [55]. Increased NKG2A expression was associated with NK cell exhaustion in COVID-19, which significantly contributes to the exhaustion of $CD8^+$ T cells [56,57]. NKG2A is commonly used as an exhaustion marker. As a result, SARS-CoV-2 mediates NKG2A overexpression in cytotoxic lymphocytes, leading to Qa-1 molecule upregulation [58]. Activation of NKG2A suppresses the release of cytokines in NK cells through transducing the expression of TIM-3 [59,60].

Moreover, IFN-γ, IL-2, granzyme B, and TNF-α levels were found to be lower in early COVID-19, with an increase in NKG2A expression in NK and $CD8^+$ T cells. In addition, NKG2A expression was found to be low in recovered COVID-19 patients, implying that NKG2A may play an important role in disease progression and the induction of NK cell exhaustion [59]. Thus, it is recommended in moderate COVID-19 to use monalizumab, an inhibiting antibody against NKG2A, to prevent risks of NK cell and $CD8^+$ T cell exhaustion, and to promote proper $CD8^+$ T and NK cell responses.

Self and non-self-discrimination via MHC binding is critical for NK cell recognition, and repetitive NK cell contact with target cells lacking MHC, whether due to viral or neoplastic etiology, is a common cause of exhaustion [60]. When SARS-CoV-2 infects epithelial cells, those cells present low expression of MHCI/MHCII due to interaction with SARS-CoV-2 through ORF8/ORF6 proteins [61–63]. Thus, it doesn't allow NK cells to recognize infected cells, while the inflammation is increasing, which induces NK cell exhaustion. Thus, the increase of inflammation without recognizing the virally infected -cell induces NK cell exhaustion in COVID-19. Fortunately, dendritic cells (DCs) play a key role in NK cell activation by producing NK-activating cytokines [64]. It can increase the expression of the molecules that control NK-DC contact and activation, such as the NKp30-activating receptor, DNAX accessory molecule-1, TNF-α, and IL-15 trans-presentation [65]. As a result, by boosting NK cell screening and detecting infected cells, which promote functional $CD8^+$ T cells, activated DCs would be a significant intervention in the immunomodulation of NK cell activity in COVID-19 [66,67].

2.3. Lymphopenia and T cell exhaustion in SARS-CoV-2 infection

Underlying mechanisms involving interaction between lymphocytes and SARS-CoV-2 and promoting severe lymphopenia are still unknown. Early reports of a rapid decline in total lymphocytes in early and intermediate COVID-19 cases were published [68,69]. As reported, lymphopenia and T cell dysfunction can be caused by one of the following: (1) antigen exposure persistence, interfering with T cell memory formation and immunological contraction mechanisms, resulting in exhaustion, (2) sustained up-regulation of ICs in $CD8^+$ T cells and NK cells. Thus, prolonged antigen exposure produces T cell fatigue, although the mechanism by which this occurs is unknown. There are some factors that contribute to the occurrence of T cell exhaustion, such as the overexpression of ICs [70]. To date, two subsets of exhausted T lymphocytes were identified in COVID-19; $CD8^+CD279^{low/medium}$ at the early and intermediate stages, which can respond to PD-1 blockade and retain semi-normal mitochondrial function; and $CD8^+CD279^{high/medium}$ at the late stage, which is terminally exhausted [71]. The inability to respond to PD-1 blockade is attributed to mitochondrial impairment. Furthermore, the overexpression of TIM-3 and PD-1 in $CD4^+$ T cells circulating in SARS-CoV-2-infected patients contributes to a shift in pathological status from asymptomatic to openly symptomatic. Following upregulation of ICs expression in T cells, IFN-γ and TNF-α levels decrease, promoting high TIGIT and HLA-DR expression in $CD8^+$ T cells [72]. Besides that, serum IL-10 levels in COVID-19 patients rise significantly during early and moderate infections [73]. Overexpression of IL-10 by $CD8a^{low}$ DCs in chronic infections was linked to $CD4^+$ T cell dysfunction. In chronic infections, neutralizing antibodies targeting the IL-10 receptor (IL-10R) promoted IFN-γ-producing $CD8^+$ T cells [74]. In the *E*-Tcl1 mouse model, lowering IL-10 levels increased $CD8^+$ T-cell proliferation, IFN-γ production, and memory cell prevalence [75]. Thus, the potential link between IL-10 release in early COVID-19 and the induction of T exhaustion could be significant.

On the other hand, the calcineurin/NFAT pathway plays an important role in T cell function. When SARS-CoV infects cells, the thymocyte selection-associated HMG box (TOX) is activated [76]. In vivo studies have shown that TOX signaling is important in the occurrence of T cell exhaustion in chronic infections such as COVID-19 [10,77]. Activation of calcineurin/NFAT signaling induces TOX expression in the nucleus. Once the pathway is initiated, sustained TOX expression causes alteration in the chromosome that changes RNA transcription, inhibiting differentiation into effector T cells and leading to overexpression of PD-1, TIM-3, CTLA-4, TIGIT, and transcription factors, such as Eomes and TCF1, which impair cytokine production and induce exhaustion status [78–80]. Altogether, all signaling pathways that enhance T cell exhaustion are suggested to promote epigenetic transcription of ICs that mediate the exhaustion status of lymphocytes.

The underlying mechanisms mediating epigenetic transcription of ICs remain to be elucidated. Assay for Transposase-Accessible Chromatin with high-throughput sequencing (ATAC-Seq) for antigen-specific $CD8^+$ T cells of patients with acute lymphocytic choriomeningitis virus (LCMV) infection that present high functional phenotype of $CD8^+$ T cells, compared to exhausted $CD8^+$ T cells with high ICs expression obtained from chronic infections (post-infection 8-27 days) and naïve $CD8^+$ T cells revealed that chromatin accessibility was significantly increased among exhausted $CD8^+$ T cells [81]. Further analysis showed that 71% of chromatin-accessible regions (ChARs) were concentrated in *Ccr7* and *Ifng* gene loci. Moreover, 44.5% of all ChARs among exhausted cells were not related to gene expression. Only 9.7% of gene expression differences were detected, indicating the change of $CD8^+$ T cells status linked to high reorganization of accessible chromatin that epigenetically induces ICs overexpression [81,82]. Another study reported that the transcription factor *Blimp-1* played a significant role in the induction of $CD8^+$ T cells exhaustion in chronic viral infections by inducing epigenetic transcription of ICs [83]. Deletion of *Blimp-1* reduced the expression of ICs and enhanced functional $CD8^+$ T cells. Moreover, persistent antigen presentation may induce epigenetic transcription of *FoxO1* that enhances sustain expression of *PD-1* and exhaustion in immune cells [84]. Moreover, a study reported that among the eight *cis*-elements that regulate the expression of *Pdcd1* (encodes PD-1), *CR-B* and *CR-C* were linked to activation of the *Pdcd1* promoter. It is noteworthy that reporter constructs that employ the PD-1 promoter but do not contain the *CR-C* region failed to trigger PD-1 expression [85]. In addition, a significant link between the exhaustion of T cells and the epigenetic transcription of *TCF1*, *IRF4*, and *TOX* in chronic viral infections was reported [10]. However, in COVID-19 this is no available data describing molecular epigenetic mechanisms regulating the expression of ICs in immune cells, confirming the urgent need for molecular studies of epigenetic changes in T cells in COVID-19.

2.4. Hypercytokinaemia and over-activation of T cells in COVID-19

Hypercytokinaemia, also known as cytokine storm syndrome (CSS), is a massive redundancy and overlap increase in inflammatory cytokine/chemokine levels that cause pulmonary dyspnea and death in COVID-19 [86]. Increased levels of proinflammatory cytokines such as IL-6, IL-2, IL-8, TNF-α, IL-1, G-CSF, and GM-CSF, as well as chemokines such as MIP1, IP10, and MCP1, are mediated by macrophages, neutrophils, and over-activated T cells [87]. CSS develops in SARS-CoV-2 infections due to secondary haemophagocytic lymphohistiocytosis elicited by a viral infection [88]. Recently, it was discovered that immune-suppressive and anti-inflammatory drugs such as hydroxychloroquine, IL-6, and IL-1β antagonists reduced hypercytokinaemia in COVID-19 patients [89]. CSS initiation causes apoptosis signaling in epithelial cells, resulting in multiorgan failure due to low oxygen levels and the induction of self-apoptosis signaling. Furthermore, as an immediate response to the viral infection, many cells undergo apoptosis, resulting in severe lung damage [90]. Lung injury induces lung fluid disequilibrium, which increases the absorption of massive fluids into lungs interstitium, reaching lungs alveoli and capillaries and resulting in pneumonia, dyspnea, and oxygen deprivation in the blood [91]. The relationship between lymphocyte exhaustion and CSS initiation is still debatable. Nonetheless, some research suggests that CSS promotes apoptosis or necrosis in T lymphocytes in COVID-19 [92]. CSS was found to induce T lymphocyte

apoptosis in COVID-19 by altering genes enriched in P53 signaling pathways, including TP53I3, STEAP3, CCNB2, BIRC5, CDK1, CTSL, CTSZ, CTSD, DDIT4, GTSE1, CTSB, NTRK1, CCNB1, RRAS, IGFBP3, TNFSF10, and RRM2 [93]. According to some reports, glucocorticoids, soluble Fas ligand (sFasL), and vascular cell adhesion molecule-1 (sVCAM-1) may play a role in inducing lymphocyte apoptosis in SARS-CoV-2 patients [94]. The relationship between CSS in COVID-19 and regulation of the apoptosis signaling P53 pathway via CCL4/MIP1B, CXCL10/IP-10, CCL3/MIP-1A, and CCL2/MCP-1, on the other hand, may have a link with T cell dysfunctionality [95]. The fusion of SARS-unique domain (SUD) and papain-like protease (SUD-PLpro) interacts with RCHY1, causing p53 degradation by promoting degradation of RCHY1-p53 and stability of RCHY1 [96], which may induce lymphocyte apoptosis and CSS activation. Overall, CSS stimulation in COVID-19 may or may not be associated with T lymphocyte dysfunction or over-activation, and more research is needed to uncover the underlying mechanisms.

2.5. Role of IL-6 in COVID-19 and cytotoxic T cell exhaustion

IL-6 is a versatile cytokine that modulates both humoral and cellular immune responses. IL-6 is also important in the cellular response to inflammation and tissue damage during chronic infections [97]. In SARS-CoV-2 infections, the SARS N protein is a powerful inducer of IL-6 secretion [98]. Furthermore, IL-6 is required for B-cell differentiation and antibody production, as well as regulation of inflammatory responses via IL-6Rb [99]. It was reported that IL-6 levels were increased in the serum of patients infected with SARS [100], MERS [101], and SARS-CoV-2. Accumulated evidence suggests a link between the SARS-CoV-2 viral load and a significant increase in IL-6 in severe COVID-19 cases [102]. As noticed, when patients with chronic diseases such as hypertension, cardiovascular diseases, cancers, and chronic renal failure become co-infected with SARS-CoV-2, the persistent overexpression of IL-6 mostly becomes a fatal factor fostering cytokine storm. Some hospitals reported that administration of tocilizumab, an anti-IL-6R antibody, in COVID-19 patients in clinical practice improved pulmonary symptoms [103]. Furthermore, the role of IL-6 in the exhaustion of $CD8^+$ T cells in COVID-19 has not been evidenced yet. The increase in T cell exhaustion in early and moderate COVID-19 was associated with an increase in IL-6 levels [104], but the link between the two factors and the underlying mechanisms remains unknown. Blocking IL-6/IL-6R improves the function of exhausted T cells by inducing cytokine release and decreasing PD-1 expression in patients with Cytomegalovirus (CMV) [105]. In addition, there is a newly published study reported that IL-6 released by macrophages promotes both M2 polarization as well as STAT3-dependent PD-1 signaling in $CD8^+$ T cells in the lung tumor microenvironment [106]. Another study suggests that IL-6/JAK1 promotes PD-L1 phosphorylation to keep it stable by activating the N-glycosyltransferase STAT3 to increase PD-L1 glycosylation [107]. As a result, more studies are needed to explore the relationship between IL-6 overexpression and $CD8^+$ T cell exhaustion in COVID-19.

3. Relationship between Th17 cells and T cell exhaustion in the SARS-CoV-2

Th17 cells play an important role in responses to viral infections and the promotion of proinflammatory responses. In COVID-19, Th17 was recognized as a major contributor to CSS, pulmonary oedema, and injury [108]. $CCR6^+$ Th17 cell subset increases in the periphery of COVID-19 severe cases [109]. This subset releases high levels of TNFα and IL-1β, which promote vascular permeability and leakage. Rapid differentiation of Th17 in part comes through the actions of IL-6 by STAT3/JAK2 dependent signaling [98]. Furthermore, Th17 cells secrete IL-17, GM-CSF, IL-21, and IL-22 in the alveoli, which promotes hyper-inflammation [110]. IL-22 contributes to the induction of mucins, serum amyloid A, fibrinogen, LPS binding protein, and anti-apoptotic proteins [110], as observed in COVID-19 infected patients. Thus, the induction of life-threatening oedema via IL-17 and IL-22 may be enriched with mucins and fibrin. Furthermore, neutrophils activate Th17, and consequently, IL-17 induces G-CSF, which works to enhance neutrophil inflammatory response [111]. Nonetheless, Th17 cells induce many inflammatory chemokines in COVID-19, including KC, MIP2A, IL-8, IP10, and MIP3A, which may attract and recruit more immune infiltrates to the alveoli. Importantly, a study of 39 COVID-19 patients found that a detected cytokine storm in plasma is accompanied by the release of TNF, IFN-γ, and IL-2, as well as differentiation of naïve T cells to Th17 or Tc17 phenotypes [22]. This alteration was linked directly with T cell dysfunction and Treg reduction. The analysis of the Th17/Treg ratio in COVID-19 patients revealed that Tregs have declined due to insufficient regulation of pro-inflammatory responses, which enhanced differentiation towards the IL-17-producing phenotype. The increase in Th17 cells mediates imbalance and uncontrollable systemic inflammation, leading to tissue damage [112]. The unique response of Th17 in COVID-19 has been linked to the exhaustion of another immune cells such as Tregs [113]. Because of the high numbers of Th17 cells in COVID-19 and the pro-inflammatory cytokines produced by Th17 cells, several clinical trials using secukinab, ixekizumab, JAK inhibitors, and ruxolitinib were conducted to reduce the proportion of Th17 cells [112,114,115]. However, the effectiveness and safety of these blockers are still debatable.

4. Immune strategies for activating SARS-CoV-2-specific T cells

Immunotherapy for SARS-CoV-2 infections is a hot focus of scientists since the beginning of the COVID-19 pandemic. Several strategies were used to stimulate specific immune responses, particularly triggering viral-specific T cells. DC-based vaccines were used early for inducing the proliferation of functional $CD4^+$ and $CD8^+$ T cells in many incurable diseases [116]. Importantly, DC-based vaccines have been tested in COVID-19 patients, as reported for a vaccination with AV-COVID-19 (Trial NCT04685603). However, the efficacy of DCs-based vaccines doesn't reach a satisfactory level as showed in previous viral infections. Stimulation of viral-specific $CD4^+$ T cells can elicit sustained activation of cytotoxic $CD8^+$ T cells and play a pivotal role in preventing viral replication, as reported in human immunodeficiency virus (HIV) [117], Hepatitis B virus (HBV) [118], and other viral diseases. Furthermore, using activated DCs and alveolar macrophages showed promises in increasing significant T cell stimulation in respiratory viral infections [119]. But in COVID-19 there was not enough innovation in the modification of DCs-based vaccine. In this context, as presented in Fig. 2, the DCs-based vaccine needs to be improved to (1) enhance the generation of SARS-CoV2-specific $CD4^+$ T cells that can boost the full immune response against virally infected cells; (2) boost the differentiation of SARS-CoV2-specific $CD8^+$ T cells; (3) inducing the activation of tolerogenic plasmacytoid DCs that has the potential to rebalance immune responses. Thus, different types of DCs such as immature cDCs, tolerogenic pDCs, DCs-reg, and DCs presenting specific viral antigens can be generated from $CD34^+$ progenitor cells, which are supposed to boost a proper response to specific viral antigens as well as keeping stable immune hemostasis by reducing hyperinflammatory responses. DCs can be transfected directly with viral-SP or concomitantly cultured with a pool of proteins or peptides derived from different strains of SARS-CoV-2 spikes for generating multi-antigen presenting DCs. These DCs can post T cell responses efficiently against multiple targets, as tested in phase 1 treatment of gastric cancer (Trials NCT03393416 & NCT03034304) [120]. DCs were modified to present multi-antigens and combined with anti-PD-1 to promote efficient multi-antigen targeting. Another approach is to use activated T cells from donors to treat severe COVID-19 cases. An important study screened spike-reactive $CD4^+$ T cells among COVID-19 patients and COVID-19 unexposed donors and discovered that 35% of spike-reactive $CD4^+$ T cells are circulating in healthy donors and 83% in COVID-19 recovered cases' blood [121]. It is

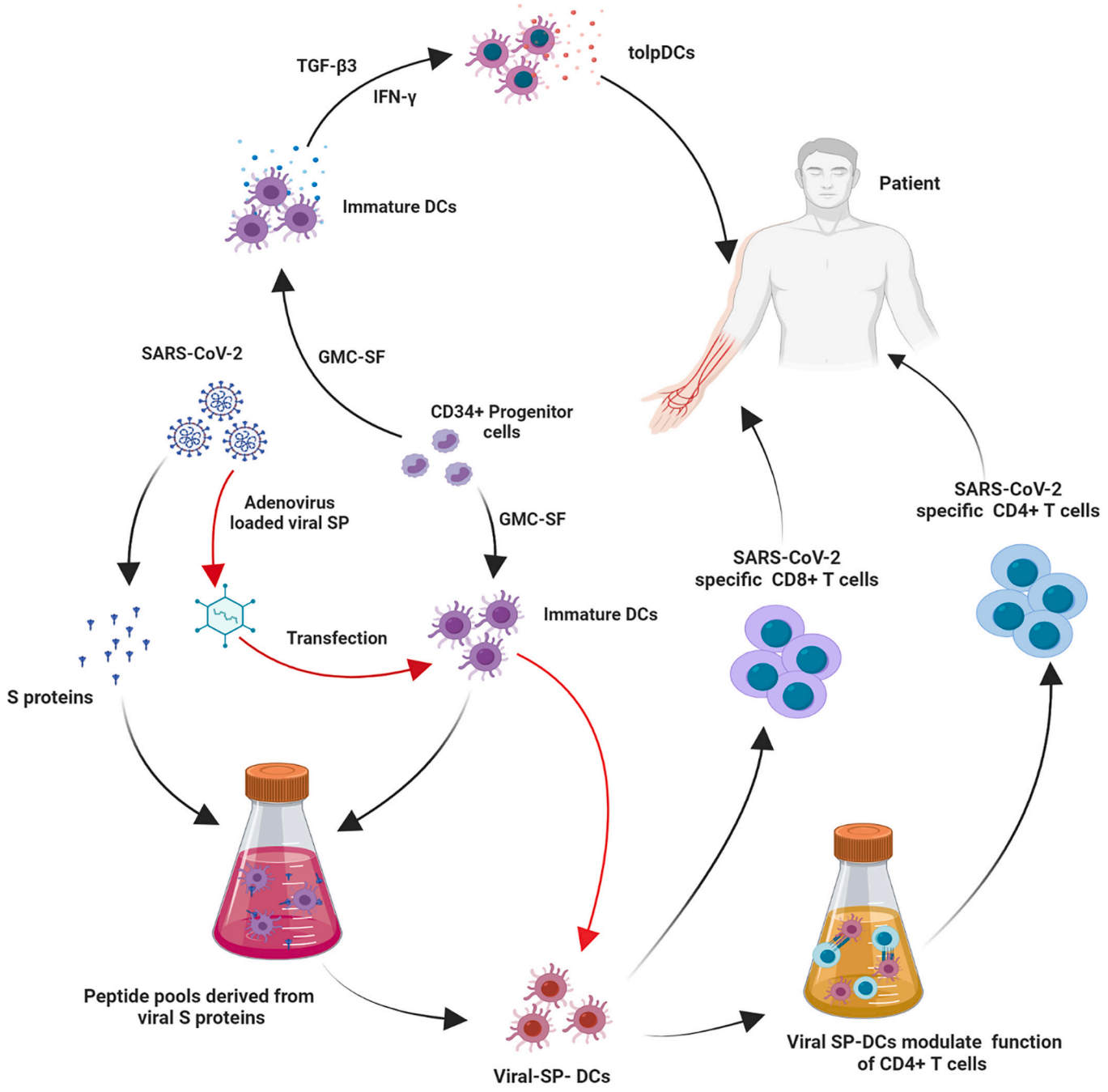

Fig. 2. Schematic diagram describes potential strategies for generating modified DCs from $CD34^+$ progenitor cells to present SARS-CoV-2-SP to T cells, leading to inducing virus-specific $CD4^+$ T cells; activating $CD8^+$ T cells; preventing exhaustion, and reducing hyper-inflammation by tolerogenic DCs phenotypes.

proposed that sorting spike-reactive $CD4^+$ T cells from donors would be an effective intervention for treating severe and moderate COVID-19. However, the causes of T cell exhaustion in COVID-19 infections may make this strategy ineffective in reducing virus replication. Nonetheless, viral-SP-overexpressing DCs are expected to generate a large number of SARS-CoV-2-specific T cells.

However, as stated above timing of suitable immune therapy intervention is very important. In the case of CSS or hyper-inflammation, the induction of inflammatory T cells would be not the proper choice. Thus, inducing immunosuppressive Tregs is required to prevent dyspnea. Thus, inducing tolerogenic plasmacytoid DCs (tolpDCs) could be an effective immune intervention in severe cases because these cells can work to increase Treg cell proliferation while decreasing hyper-inflammation in the lungs [122]. As a result, using tolpDCs for severe and moderate COVID-19 infections could improve breathing due to reducing inflammatory mediators by activating $foxp3^+$ Tregs [123]. tolpDCs can be injected directly into the peritoneum or any other location near lymph nodes that are supposed to induce Treg differentiation and proliferation. As a result, tolpDCs for inducing $foxp3^+$ Tregs could contribute to the first line of immune intervention to treat COVID-19 by rebalancing immune responses. After that, stimulation of effector T cells would be the required step for effective immunotherapy of COVID-19.

5. Conclusion

It is evident that SARS-CoV-2 activates critical immunomodulation mechanisms, which are likely to result in induction of imbalanced immune responses of both innate and adaptive immune cells. Several articles reported exhaustion and over-activation of immune cells at different stages of COVID-19, which suggests the need for time and COVID-19 stage consideration before immune intervention. Thus, the interaction between virus, host cells, and immune responses is very important to manage infection initiation, progression, and immune exhaustion. Exhaustion of T cells, compared to over-activation in COVID-19, could be caused by different factors such as epigenetic induction of ICs, persistent overexpression of multiple antigens, an interaction between different immune responses, and response to activation of a special type of Th17 cells. However, to date, the link between exhaustion of immune cells and the induction of ICs remains controversial. Few studies reported expressions of ICs such as PD-1, LAG3, and TIM-3 in cytokine-producing T cells and concluded no relationship between the exhaustion of T cells and ICs in COVID-19. On the other hand, different clinical studies reported the significant relationship between T cell exhaustion and the expression of ICs, which promote an acceleration of COVID-19 virulence. By tracking previous studies, the role of ICs in immune cell exhaustion and COVID-19 virulence was clearly evidenced. However, recording cytokines released from exhausted T cells needs further investigation. Hence, the importance of immune modulation in the induction of persistent exhaustion of immune cells and over-activation of the immune response needs further studies in human and animal models to reach a proper understanding of the interaction of SARS-CoV-2 with the immune system. Thus, immunotherapy of COVID-19 will be more specific and efficient.

Data availability statement

This part is not applicable.

Contribution

Article conception and design: M.A, E.E.; manuscript preparation: M. A, E.E. Revising manuscript and corrections; E.E; Drawing Figures: M.A; Supervising the whole work; E.E, M.A. Both authors reviewed the whole work and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare that no financial or non-financial conflicts of interest are related to this work.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clim.2022.109177.

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