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T-cell dysregulation in COVID-19

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ABSTRACT

T-cells play key roles in immunity to COVID-19 as well as the development of severe disease. T-cell immunity to COVID-19 is mediated through differentiated $CD4^+$ T-cells and cytotoxic $CD8^+$ T-cells, although their differentiation is often atypical and ambiguous in COVID-19 and single cell dynamics of key genes need to be characterized. Notably, T-cells are dysregulated in severe COVID-19 patients, although their molecular features are still yet to be fully revealed. Importantly, it is not clear which T-cell activities are beneficial and protective and which ones can contribute to the development of severe COVID-19. In this article, we examine the latest evidence and discuss the key features of T-cell responses in COVID-19, showing how T-cells are dysregulated in severe COVID-19 patients. Particularly, we highlight the impairment of FOXP3 induction in $CD4^+$ T-cells and how the impaired FOXP3 expression can lead to the differentiation of abnormally activated (hyperactivated) T-cells and the dysregulated T-cell responses in severe patients. Furthermore, we characterise the feature of hyperactivated T-cells, showing their potential contribution to T-cell dysregulation and immune-mediated tissue destruction (immunopathology) in COVID-19.

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1. Text

T-cells are required to induce immune responses specific to SARS-CoV-2 by recognizing viral antigens through their antigen receptor, T-cell receptor (TCR) [1]. Since TCR is highly variable due to the random recombination of the TCR genes, each antigen can only be recognized by a small number of T-cells [2,3]. Since T-cells recognize antigens as peptides bound to Major Histocompatibility Complex (MHC), T-cells can recognize not only structural proteins such as spike (S) and nucleocapsid (N) proteins but also non-structural proteins including ORF3a and ORF7 [1]. Once recognizing a viral antigen, $CD4^+$ T-cells are activated and can differentiate into helper T-cell subsets through the activities of transcription factors and cytokines specific to each subset. $CD4^+$ T-cell help promotes the maturation of B-cells, which undergo affinity maturation and class-switching of virus-specific antibodies through the action of activation-induced cytidine deaminase (AID) [4]. Meanwhile, $CD8^+$ T-cells can get primed with the help of $CD4^+$ T-cells and differentiate into cytotoxic T-cells, which produce cytotoxic molecules such as granzymes and perforins upon recognizing antigen and thereby induce the apoptosis of virus-infected cells [1,5]. Therefore, T-cells play central roles in viral infections including COVID-19, and thus, it is not surprising that T-cells are dysregulated particularly in severe COVID-19 patients. This article will show the evidence of T-cell dysregulation in severe COVID-19 disease and discuss underlying molecular mechanisms.

1.1. Lymphopenia and T-cell reduction in COVID-19

Severe COVID-19 patients show the reduction of all lymphocyte subsets including $CD4^+$ and $CD8^+$ T-cells, NK cells, and B cells (i.e. lymphopenia) [6–8], while monocytes and granulocytes increase in circulation [8]. COVID-19 patients show the increase of serum cortisol [9], which is suggested to be a cause of lymphopenia in SARS [10], because corticosteroid treatment can also transiently reduce lymphocyte numbers while increasing neutrophils and monocytes in circulation [11,12]. In addition, T-cells in severe

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COVID-19 patients highly express activation markers as discussed below. Thus, it is likely that other factors also contribute to the T-cell reduction in COVID-19.

T-cell numbers are regulated by proliferation and apoptosis during homeostasis [13], and accordingly, T-cell reduction in COVID-19 can be due to either or both of increased apoptosis and reduced proliferation rates. While Fas expression is increased in T-cells from COVID-19 patients [14], T-cell data in Zhu et al. showed that Fas, FasL, and Caspase-3 [15], which play key roles of T-cell apoptosis, were not significantly increased in COVID-19 patients [16]. Interleukin (IL)-7 is a key cytokine for T-cell homeostasis, sustaining the naïve T-cell pool [17]. However, serum IL-7 levels are increased in severe COVID-19 patients [18], indicating that the IL-7-mediated compensatory mechanism is operating normally. IL-15 is important for maintaining the size of the $CD8^+$ T-cell and memory T-cell pool [17] and could play a role in T-cell homeostasis in COVID-19, although data for IL-15 in COVID-19 is limited. Interestingly, T-cell numbers are negatively correlated with the serum concentration of cytokines including IL-6 and IL-10 in COVID-19 patients [7]. IL-6 is primarily produced by macrophages, dendritic cells (DCs), B-cells, and T-cells and can promote the proliferation of T-cells in inflammatory conditions [19]. IL-10 is produced by a wide range of cells including DCs, macrophages, B-cells, and T-cells including T-helper type 2 (Th2) and regulatory T-cells (Treg). IL-10 can suppress the proliferation of $CD4^+$ and $CD8^+$ T-cells in some contexts [20] while enhancing T-cell proliferation in the presence of other γ-chain cytokines i.e. IL-2, IL-4, IL-7, and IL-15 [21]. Given the increased cytokine production in severe COVID-19 patients, it is unlikely that the elevated IL-10 levels is the cause of T-cell reduction. These collectively suggest that T-cell reduction is a consequence of the activation of various innate and adaptive immune cells, which inevitably leads to the activation of T-cells as well.

1.2. Interferon and cytokine responses to COVID-19

SARS-CoV-2-infected epithelial cells can detect viral RNA by cytosolic sensors including RIG-1 and MDA5 and produce type-I interferons (IFNs), which induces IFN-mediated anti-viral responses [22]. Notably, in comparison to other respiratory viruses, SARS-CoV-2 induces lower levels of type-I IFNs (IFN-α, IFN-β) and type-III IFN (IFN-λ) and higher chemokine expression in primary human bronchial epithelial cells in comparison to other common respiratory viruses [23]. Still, IL-1β and type I and type III IFNs are modestly induced in active COVID-19, while persisting and even increased during the recovery phase [24].

Type-I IFNs not only induce cell-intrinsic anti-viral states in infected and neighbouring cells, but also promote innate immune responses. In viral infections, DCs, particularly plasmacytoid DCs (pDCs), play key roles in inducing innate immune responses following IFN responses, as pDCs can rapidly produce large amounts of type-I IFNs upon viral infection [25]. Importantly, pDCs can produce type-I IFNs not only when they are infected but also when adjacent cells are infected and produce type-I IFNs. However, Laing et al. showed that pDCs were markedly reduced in PBMCs from severe COVID-19 patients in comparison to moderate patients and healthy controls [26].

In addition, type-I IFN signalling promotes the maturation of DCs, increasing the expression of MHC and CD80/86 [27], the latter of which enhances the activation of T-cells as discussed below. In severe COVID-19 patients, type-I IFN response is impaired in peripheral mononuclear blood cells (PBMCs) and BAL fluid, showing reduced type-I IFN production [28,29]. Similarly, in SARS-CoV-1, delayed type-I IFN responses can promote the development of a severe disease through the accumulation of inflammatory monocytes-macrophages, which leads to impaired T-cell responses [30]. In fact, circulating monocytes from severe patients express more IL-1β and TNF-α [31]. In addition, macrophages in bronchoalveolar lavage (BAL) fluids from severe COVID-19 patients express higher levels of IL-1β, IL-6 and TNF-α than moderate patients [32]. Intriguingly, the chemokine CCL3 (MIP1A) is increased in both serum and BAL fluid-derived T-cells from severe COVID-19 patients [18,33]. Thus, the combination of the impaired production of type-I IFNs and the increased production of proinflammatory cytokines may contribute to the development of the severe disease [22].

Collectively, the delayed IFN responses in COVID-19 can result in the increased proinflammatory cytokine responses, changing the dynamics of antigen presentation and cytokine production in innate immune cells, which may contribute to the dysregulation of T-cell responses.

1.3. T-cell activation in COVID-19

Antigen presenting cells such as mature DCs present antigens to T-cells on their MHCs, and highly express CD80/CD86, which interacts with CD28 on T-cells [34]. Then, antigen-specific T-cells receive TCR signals and costimulatory signals, resulting in their activation. Activated T-cells produce IL-2 while expressing the IL-2 receptor, which is composed of α (CD25), β (CD122), and γ chains [35]. CD25 is particularly important as an inducible protein to produce the high-affinity IL-2 receptor. Thus, CD25-expressing activated T-cells receive IL-2 signalling, which further promotes their proliferation and differentiation.

Interestingly, soluble CD25 is increased in COVID-19 patients [24,69], and a study showed the increase of IL-2 as well [18]. Since both IL-2 and IL-2 receptors are expressed predominantly by T-cells, it is possible that the positive feedback loop for IL-2 signalling in T-cells is established in some patients. However, it is not known whether this is protective or contributes to the pathology of COVID-19. In normal situations, IL-2 signalling can induce FOXP3, which stops the IL-2 response as a negative feedback mechanism [36], but this FOXP3 induction is impaired in severe COVID-19 as discussed below. Importantly, therapeutic administration of recombinant IL-2 in human patients can induce vascular leak syndrome, which is characterized by multiple organ failure due to increased vascular permeability [37].

Activated $CD4^+$ and $CD8^+$ T-cells also increase the expression of the proliferation marker Ki67 and the activation markers CD38 and HLA-DR. Such T-cells will be identified in non-naïve T-cell fractions, which include activated, effector, and memory T-cells. Interestingly, circulating non-naïve $CD4^+$ and $CD8^+$ T-cells show higher expressions of Ki67, HLA-DR, and CD38 in COVID-19 patients in comparison to both recovered patients and healthy donors [38]. This indicates that a significant proportion of circulating T-cells react to the infection, which suggests that, in addition to the clonal expansion of SARS-CoV-2-specific T-cells, a broad range of the T-cell repertoire including self-reactive T-cells may be expanded in COVID-19. Currently, methods are limited for the analysis of the TCR-repertoire, but key resources may be obtained by single cell TCR-sequencing [39] of COVID-19 patients and the investigation of complementarity-determining region 3 (CDR3) of TCRs in each MHC haplotype [40] to understand the dynamics of virus-specific T-cells and self-reactive T-cells.

1.4. T-cell differentiation in COVID-19

Th1 cells, which produce IFN-γ and TNF-α [41], are important for viral infections, although the role of Th1 response in COVID-19 is not clear. SARS-CoV-2 spike (S) protein-specific T-cells are induced during the acute phase of COVID-19 and these cells produce IFN-γ [42]. However, another report showed that $CD4^+$ T-cells had

impaired IFN-γ and TNF-α production in severe COVID-19 patients [43], although severe COVID-19 patients show higher levels of serum IL-12 [8], which potently induces Th1 differentiation [41]. Lucas et al. showed that severe COVID-19 patients had higher serum levels of IFN-γ and IL-17A, the latter of which is produced by Th17 cells [8]. Th17 plays a key role in autoimmunity and infections including COVID-19 [45]. Notably, IL-6 signalling induces Th17 differentiation through activating STAT3 and inducing Th17 transcription factors including ROR-γt and AHR [46]. Intriguingly, T-cells from COVID-19 patients express higher levels of the IL-6 receptor than those from Influenza patients and healthy controls [16]. In addition, some T-cells from COVID-19 patients are identified as non-classical Th1 cells that highly express the Th17 markers CD161 and IL-1 receptor type I (IL-1RI) [24]. De Biasi et al. showed that not only IFN-γ but also Th2 cytokines including IL-4, IL-10, and IL-13 were increased in COVID-19 patients with pneumonia [45], while Schultheiβ et al. showed only marginal increase of IFN-γ in serum from COVID-19 patients [24]. Kalfaoglu et al. showed that both of the transcription factors *TBX21* (T-bet) and *GATA3*, which induce Th1 and Th2 differentiation, respectively, were induced in activated $CD4^+$ T-cells in BAL fluids from COVID-19 patients. In addition, *IL4R* and *MAF*, which are required for Th2 differentiation, were more highly induced in BAL-derived $CD4^+$ T-cells from severe COVID-19 patients [33]. Collectively, it is likely that T-cells show mixed Th1, Th2, and Th17 responses in COVID-19, and it is yet to be revealed which Th response is the most protective.

$CD4^+$ T-cell responses to S-protein correlated with the concentration of the anti-SARS-CoV-2 IgG and IgA titres in convalescent patients [1], showing the importance of the T-cell help for B-cell maturation in recovery from COVID-19. This is most likely mediated by a subtype of $CD4^+$ T-cells, T-follicular helper cells (Tfh), which provide the T-cell help that is required for B-cell differentiation and the affinity maturation of antibodies [47]. Tfh cells differentiate from antigen-reactive T-cells in lymph nodes. Tfh are identified by the expression of CXCR5 and PD-1 and are typically found in germinal centres (GCs). Some Tfh can be found in circulation (circulating Tfh, cTfh) and are identified as $CXCR5^+CD45RA^-$ $CD4^+$ T-cells ($CD45RA^-$ indicates antigen experienced T-cells). In COVID-19, cTfh cells are induced in COVID-19 patients [38,48] including severe patients [49]. Interestingly, cTfh upregulate CCR6, a marker of Th17 [50], upon stimulation with the S-protein of SARS-CoV-2, thus showing Th17-like cTfh features [51]. On the other hand, Kaneko et al. showed that GCs were not formed in lymph nodes and that BCL-6-expressing Tfh were reduced in COVID-19 [52]. In addition, Kalfaoglu et al. showed that *BCL6* and Th17 genes (including *RORC*, *IL17A*, and *CCR6*) were repressed in BAL fluid-derived $CD4^+$ T-cells from severe COVID-19 [33]. Collectively, these suggest that uncharacterised T-cell differentiation, which partially resemble Th17 and Tfh, may be important to control the infection.

$CD8^+$ T-cells can be primed in lymph nodes and kill virus infected cells through the release of cytotoxic molecules such as perforin and granzyme B [53]. Interestingly, after the recovery from COVID-19, patients with mild disease sustain SARS-CoV-2-specific $CD8^+$ T-cells than patients with severe disease, suggesting that the induction of potent $CD8^+$ T-cell responses is protective [54]. However, during active disease, $CD8^+$ T-cells can produce higher levels of perforin and granzyme B in severe COVID-19 patients than in mild patients and healthy donors [43,49,55]. Interestingly, Westmeier et al. showed that $CD8^+$ T-cells from aged COVID-19 patients failed to produce perforin and granzymes [56], although further studies are required to confirm the result. Notably, $CD8^+$ T-cells in severe COVID-19 patients had higher frequencies of $PD\text{-}1^+$ cell subsets [7,49]. Although PD-1 is often used as a marker to identify exhausted T-cells, $PD\text{-}1^+CXCR5^+CD8^+$ T-cells are important anti-viral effectors in the lymphocytic choriomeningitis virus (LCMV) infection model [57]. Further studies are required to determine whether $PD\text{-}1^+CD8^+$ T-cells in COVID-19 are protective or contribute to the development of severe disease.

1.5. FOXP3 repression and hyperactivated T-cells in COVID-19

FOXP3 is widely recognized as the Treg-specific transcription factor, and FOXP3-expressing T-cells can suppress T-cell responses [58,59]. In humans, ~5% of $CD4^+$ T-cells highly express FOXP3 [60,61]. Notably those $FOXP3^{high}$ Treg highly express CD25 and downregulate IL-7 receptor α (CD127) [61]. The majority of such naturally-occurring $FOXP3^+$ Treg recognize self-antigens or microbiome antigens [62]. In fact, $FOXP3^+$ Treg regularly receive TCR signals *in vivo* [63] and show higher Ki67 expression, indicating their activated and proliferating status [61]. The expression of both CD25 and FOXP3 is dynamically regulated *in vivo* [60,63] and is controlled by IL-2 and TCR signals [64].

When TCR and TGF-β signals are available, IL-2 signalling in activated T-cells promotes not only their survival and proliferation but also the expression of the *FOXP3* gene [65]. FOXP3 represses *IL2* transcription, inducing hyporesponsiveness (anergy) to TCR signals [66]. Importantly, natural $FOXP3^+$ Treg also further upregulate *FOXP3* transcription through its autoregulatory transcriptional loop during inflammation, increasing the expression of Treg-associated molecules including CD25 and CTLA-4, which is required for their suppressive function [67]. Thus, FOXP3 works as a negative feedback mechanism for suppressing T-cell activation whether in Treg and in non-Treg (Fig. 1).

FOXP3 expression in circulating $CD4^+$ T-cells is higher in convalescent COVID-19 patients than unexposed individuals [68]. On the other hand, the frequency of Treg in circulation is reduced in severe patients [69], although results are variable between studies [26]. This suggests that, paradoxically, FOXP3 induction is favourable to the outcome in some patients, suggesting a role of FOXP3 in anti-viral T-cell immunity. Intriguingly, a significant percentage of $CD4^+$ T-cells highly express CD25 while FOXP3 expression is repressed in the lung of severe COVID-19 patients [33]. Those $CD25^+$ $FOXP3^-$ T-cells highly express CTLA-4, GITR, and other activation/Treg markers, suggesting that their differentiation into Treg is prematurely blocked (Fig. 1). In addition, Jeannet et al. showed that severe patients in Intensive Care Unit (ICU) showed sustained reduction of all lymphocyte subsets including T-cells, while the expression of CD25, CTLA-4, and PD-1 in $CD4^+$ T-cells was increased, although their study did not analyse FOXP3 expression [6].

Although the mechanism of FOXP3 repression in severe COVID-19 is yet to be revealed, IL-6 produced by macrophages and monocytes may contribute to the repression. IL-6 signalling activates STAT3, which antagonises STAT5 activities and thereby represses IL-2-mediated *FOXP3* transcription [70]. As discussed above, T-cells in severe COVID-19 show higher IL-6 receptor expression and thus are considered to be sensitive to IL-6 in the microenvironments. In addition, our scRNA-seq analysis showed that IL-2 was not detected in BAL fluid-derived $CD4^+$ T-cells from severe COVID-19 patients [33], and critically ill patients show reduced serum IL-2 [71]. These suggest that IL-6 overproduction and IL-2 deprivation contribute to *FOXP3* repression in severe COVID-19.

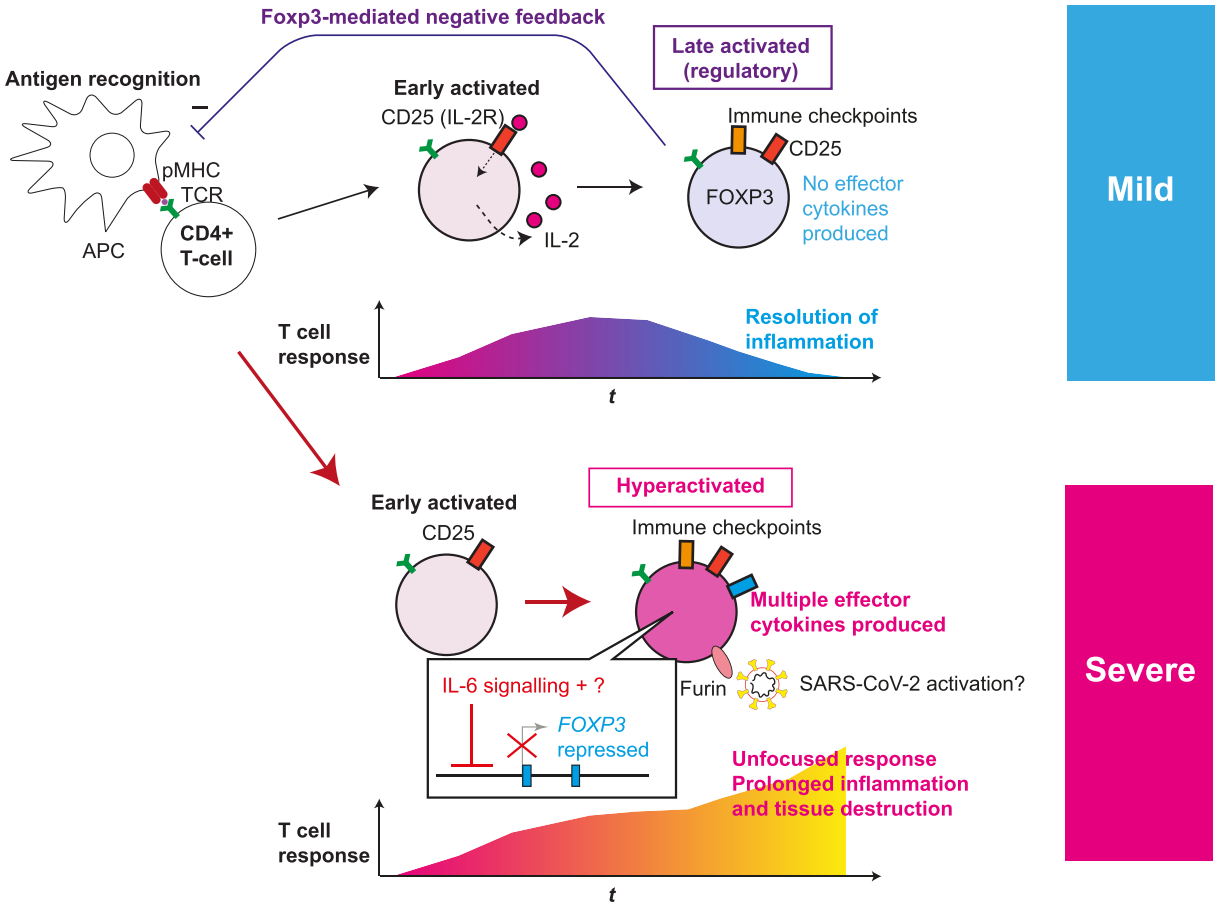

Fig. 1. Roles of T-cell hyperactivation in the lung of severe COVID-19 patients. The fates of activated T-cells in mild and severe COVID-19 patients are depicted. Antigen-presenting cells (APC) present antigens as peptide-MHC complex (pMHC) to $CD4^+$ T-cells, which triggers T-cell receptor (TCR) signalling and subsequent activation and differentiation processes. Initially, early activated T-cells start to produce CD25 and IL-2, establishing a positive feedback loop for T-cell activation and proliferation. Subsequently the fates of activated T-cells are different in mild and severe COVID-19 patients. (Upper panel) In normal conditions and mild patients, IL-2 signalling enhances *FOXP3* transcription in a part of activated T-cells. In addition, the expression of immune checkpoint molecules such as CTLA-4 is increased. Meanwhile, some T-cells can differentiate into Tfh and Th cells (not shown). $CD25^+CTLA\text{-}4^+FOXP3^+$ T-cells can consume and occupy immunological resources including IL-2 and CD28 signalling, and thereby suppress T-cell activation, leading to resolution of inflammation. (Lower panel) In severe COVID-19, activated T-cells fail to express FOXP3 while further enhancing the expression of CD25 and immune checkpoint molecules, producing multiple Th cytokines and showing the features of hyperactivated T-cells. *FOXP3* repression is likely due to the increased IL-6 availability and undefined factors. In addition, $CD25^+$ hyperactivated T-cells produce FURIN, which may further enhance the viral infection, promoting prolonged inflammation and tissue destruction. Figure modified from Ref. [33].

FOXP3 inhibition generally induces inflammation, although this may not be beneficial in infections [36]. Rather, the inhibition of FOXP3 induction can lead to unfocused T-cell responses that induce immunopathology (i.e. immune-mediated tissue destruction) and ineffective antiviral T-cell response. For example, in a mouse model of herpes simplex infection, the depletion of $FOXP3^+$ Treg induces strong inflammation and prolongs the infection [72]. Similarly, Treg depletion results in increased mortality in a murine model of coronavirus-induced acute encephalitis [73].

In addition, depletion of $FOXP3^+$ Treg can induce T-cell responses to self-antigens, which lead to the development of autoimmunity [59]. Interestingly, severe COVID-19 patients show B-cell repertoire features previously described in active systemic lupus erythematosus (SLE) patients, a systemic autoimmune disease [74]. Here it is worthwhile to note that active SLE patients have reduced $FOXP3^{high}$ Treg in circulation [61]. These collectively suggest that the impairment of FOXP3 induction in severe COVID-19 induces autoimmune-like T-cell responses to self-antigens, which deplete immunological resources that could have been used by virus-specific T-cells.

Interestingly, $CD25^+$ T-cells in severe COVID-19 patients specifically express the protease FURIN [33]. FURIN and the serine protease TMPRSS2 can cleave spike (S) protein of SARS-CoV-2 and enhance the viral entry into human cells [75]. FURIN is expressed by Treg and a knockout study showed that FURIN expression is required for Treg-mediated immune suppression [76]. In addition, FURIN expression is induced in T-cells by TCR signalling *in vivo* and *in vitro* [33], and therefore, $FOXP3^+$ Treg and highly activated $CD25^+CD4^+$ T-cells could potentially enhance the activation of S protein in inflammatory tissues. Since a larger proportion of macrophages produce FURIN and the number of $FOXP3^-CD25^+CD4^+$ T-cells is small in each individual, the contribution of FURIN expression in those T-cells towards enhancing viral entry, if any, could be mediated through either SARS-CoV-2 infection of T-cells themselves or the enhancement of viral entry into DCs with which antigen-specific T-cells may intimately interact [77]. Although T-cells do not express ACE2, it is possible that SARS-CoV-2 enters non-ACE2 expressing cells using alternative receptors [78], and further investigation is needed.

Collectively, $FOXP3^-CD25^+CD4^+$ T-cells in severe COVID-19 patients are considered to be abnormally activated (hyperactivated), failing to differentiate into specific T-cell subsets. Their

activation and differentiation may also be prematurely stopped at an early activation stage and contribute to the infection and pathogenesis (Fig. 1).

2. Perspective and conclusion

FOXP3-mediated negative regulatory mechanisms of T-cell activation are impaired and $CD25^+$ hyperactivated T-cells are induced in severe COVID-19 patients. In addition, atypical T-cell differentiation seems to occur in COVID-19, producing T-cells that partially resemble Th1, Th2, Th17 and Tfh but lack their cardinal features. SARS-CoV-2 can induce abnormal responses of macrophages and DCs through infection, which control the differentiation of hyperactivated T-cells, possibly through the impaired type-I IFN response and the production of cytokines including IL-6.

Key outstanding questions include: (1) how the impaired FOXP3 induction can lead to the development of severe COVID-19, in which dysregulated T-cell responses dominate protective immune responses and induce immunopathology; (2) which T-cell subsets are protective, and which genes are important for effective T-cell immunity against COVID-19; (3) in addition to $CD25^+$ hyperactivated T-cells, which T-cell subsets are pathogenic in the severe disease and which molecules can be targeted to block the aberrant T-cell responses (4) whether and how impaired IFN responses lead to T-cell dysregulation. Single cell-level analysis, particularly the analysis of TCR repertoires and antigen-specific T-cells will be important for revealing the dynamics of virus-specific and tissue-specific T-cell activities. Furthermore, mechanistic understanding of protective T-cell immunity to COVID-19 and their dysregulation will be key to improved prevention and treatment strategies for COVID-19.

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