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Review article

SARS-CoV-2 infection: The role of PD-1/PD-L1 and CTLA-4 axis

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ABSTRACT

The outbreak of SARS-CoV-2 in Wuhan of China in December 2019 and its worldwide spread has turned into the COVID-19 pandemic. Respiratory disorders, lymphopenia, cytokine cascades, and the immune responses provoked by this virus play a major and fundamental role in the severity of the symptoms and the immunogenicity which it causes. Owing to the decrease in the inflammatory responses' regulation in the immune system and the sudden increase in the secretion of cytokines, it seems that an investigation of inhibitory immune checkpoints can influence theories regarding this disease's treatment methods. Acquired cell-mediated immune defense's T-cells have a key major contribution in clearing viral infections thus reducing the severity of COVID-19's symptoms. The most important diagnostic feature in individuals with COVID-19 is lymphocyte depletion, most importantly, T-cells. Due to the induction of interferon-γ (INF-γ) production by neutrophils and monocytes, which are abundantly present in the peripheral blood of the individuals with COVID-19, the expression of inhibitory immune checkpoints including, PD-1 (programmed death), PD-L1 and CTLA4 on the T-cells' surface is enhanced. The purpose of this review is to discuss the functions of these checkpoints and their effects on the dysfunction and exhaustion of T-cells, making them almost ineffective in individuals with COVID-19, especially in the cases with extreme symptoms.

1. Introduction

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as the fifth pandemic in the 21st century and as the third human coronavirus epidemic following SARS-CoV in 2002 and the Middle East Respiratory Syndrome coronavirus (MERS-CoV) in 2012 with an increasing worldwide mortality has raised major concerns and warnings for the universe and the World Health Organization (WHO) since it drew attention for the first time in Wuhan, China in December 2019 [1]. SARSCoV-2 the causative pathogen of coronavirus disease 2019 (COVID-19), belongs to the *Coronaviridae* family and causes acute respiratory infections and gastroenteritis in adults and infants and approximately caused 3–6% mortality [2–5]. SARS-CoV-2 is a single-stranded RNA (ss-RNA) virus with the largest genome among RNA-viruses with a length of 29,903 nucleotides. The virus is coated with prominent, crown-like proteins on its surface that induces immune responses [6–8]. Similarly, this virus, like the two other viruses, SARS-CoV and MERS-CoV, utilize ACE2 (angiotensin-converting enzyme 2) as a receptor to enter the target cells [3,6]. SARS-CoV-2 infection has been shown to occur in three stages: 1. Clinically asymptomatic incubation period, in which there is a possibility of transmission to other susceptible individuals; 2. The period with mild symptoms affect the upper respiratory tract with flu-like symptoms; 3. The period of developing severe symptoms, which occurs in 5% of the patients. Critical conditions such as sepsis and multiple organ or tissue failure occur, and can lead to acute severe pneumonia, acute respiratory distress syndrome (ARDS) and even death [9–11]. Based on evidence, the acquired immune system plays a major role in reducing the rate of replication and the spread of the virus.

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Infection with SARA-CoV-2 in the tissues with high epithelial ACE2 expressions can also lead to extensive tissue damages; as a result, it causes severe inflammation and subsequently damages the target tissues; including kidneys and lungs [12–14]. In addition to dyspnea, hypoxemia, acute respiratory syndrome, and cytokine secretion syndrome, advanced lymphopenia, mostly in T-cells, has been reported in COVID-19 [15]. During the SARS-CoV-2 infection, there is a positive relationship between the destruction of T-cells and the increased expression of inhibitory immune checkpoint molecules on their surfaces [16]. These inhibitory immune checkpoint molecules have been reported to regulate T-cells' destruction during chronic viral infections, and in malignancies, as well as acute viral infections including Ebola and Hantavirus [17]. A number of these immune inhibitory checkpoint molecules have been reported to belong to the family of CD28 receptors and their associated ligands; which in the co-stimulatory pathways, such as CD28 and inducible T-cell co-stimulator (ICOS) or CD278, lead to the extension of immune responses; in addition, they can also participate in co-inhibitory pathways such as cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and programmed cell death protein 1 (*PD-1*) [18]. It has also been shown that the serum levels of all the molecules besides programmed cell death ligand (PD-L)-2 gets remarkably higher in severe patients compared to mild and asymptomatic individuals [17]. Furthermore, In a 2012 study regarding the PD-1/PD-L1 axis in acute viral infections affecting lower respiratory tract conducted by Erickson et al.; it has been shown that this pathway impairs the activity of CD8+ T-cells in the human respiratory system [19,20], also, dendritic cells prevent the activity of T-cells in acute viral infections by expressing high levels of PD-L1 on their surfaces [20–22].

The significance of monitoring the immune defenses in COVID-19's pathogenesis is undeniable as it is not yet clear whether a person's vulnerability is more related to the suppressive effects of the immune responses or, conversely due to overactivity of the immune system. Thus, investigating the immune system-regulating checkpoints seems to provide effective solutions to the treatment of COVID-19 [23]. The most important complication in the treatment with checkpoint inhibitors (CI) including PD-1, PDL-1, and CTLA-4, is the occurrence of checkpoint inhibitor pneumonitis (CIP) [24]. Moreover, cytokines including interleukin (IL)-6, and IL-2, are elevated in the individuals with COVID-19. Extreme levels of inflammatory factors including reactive protein C (CRP) and lymphopenia, especially a remarkable reduction in CD4+ and CD8+ T lymphocyte cell counts are also present in the patients affected by the virus, that this even shown in death individuals [25–27] (Table.1).

2. Programmed cell death protein 1 (PD-1)

Programmed cell death protein 1 (PD-1) or CD279 (cluster of differentiation 279), is present on the cells' surface, which causes down regulation of the immune system responses, suppresses T-cells' inflammatory activity, and enhances self-tolerance [28]. PD-1 as an immune checkpoint protein, increases the apoptosis (programmed cell death) of specific T-cells in lymph nodes and decreases the apoptosis of regulatory T-cells (anti-inflammatory, suppressive T-cells) [29]. PD-1 is displayed more on the surface of CD8+ and CD4+ T-cells. The PD-1/PD-L1 pathway inhibits T-cells' function; this inhibitory function is achieved by binding PD-1 to its ligands (PD-L1 and PD-L2), that expressed on the surface of peripheral tissues, and tumor cells, also the expression of PD-L1 controls IFN-γ-secreting T-cells [30]. Moreover, serum levels of glucocorticoid-induced tumor necrosis factor receptor (GITR), soluble 4-1BB (s4-1BB) or CD137, soluble T cell immunoglobulin and mucin domain 3 (sTim-3), soluble CD27, soluble lymphocyte activating 3 gene (sLAG-3), sPD-1, sCD28, sCTLA-4, soluble B and T lymphocyte attenuator (sBTLA), CD270 and sCD80; as well as the level of GITR, Tim-3, CD27, PD-1 and LAG-3 on CD4 and CD8 T-cells' surface were significantly up-regulated in severely symptomatic patients compared to milder conditions [17]. Therefore, the inhibition of PD-1/PD-L1 axis is expected to increase T-cells' activity and potentially detect and destroy the tumor cells. PD-1 participates in the down-regulation of T-cell's response, and its high expression on CD8+ T-cells in chronic infections or cancers, indicates that it is an important indicator of T-cell exhaustion [31]. It has been reported that, in the case of chronic viruses, continuous PD-1 expression causes T-cell exhaustion, and impairs the ability of killing the infectious cells [32]. It is important to evaluate the specific antigen responses of CD8+ and CD4+ effector T-cells in patients with COVID-19; because CD8+ T-cells secrete IFN-γ and CD4+ T-cells secrete Th-1 and Th-2 cytokines, which along with cytotoxic T-cells play a major role in removing and clearing viral particles, eliminating the viral infections [33–35]. The adumbration of patients with COVID-19 is characterized by a diminished lymphocyte percentage, with a similar proportion of CD4+ and CD8+ T-cells. The quantity of T-cells, mostly CD8+ T-cells, presenting high expression rates of late activity marker CD25 and exhaustion marker PD-1 increases. Therefore, SARS-CoV-2 is able to make changes by modifying the acquired immune system, including B and T cells [36].

PD-1's expression on the surface of monocytes and the activation of it by binding the PD-L1 ligand, induces the secretion of IL-10, and lead to inhibiting the activity of CD4+ T-cells [37].

Although the PD-1/PD-L1 axis is involved in persistent viral infections but their importance in acute viral infections has not yet been investigated and is still unknown due to the ineffective regulation of these checkpoint molecules in T-cell dysfunctions [31,38].

It has also been suggested that, the patients with COVID-19, show increased CD95 (Fas) and PD-1 expressions in both CD4+ and CD8+ T-cells. This also indicates the association of these regulatory molecules with the apoptosis of antigen-activated T-cells during the COVID-19 infection, this events that lead to decreased CD4+ T-cell numbers and cause a lower percentage of naive T-cells [39]. Moreover, COVID-19 patients often demonstrate lymphocytopenia and decreased counts of lymphocytes, B and Th cells; however, they have great levels of IL-6, IL-10 and tumor necrosis factor (TNF)-α and promoted expressions of exhaustion markers including PD-1 and T-cell immunoglobulin mucin-3 (Tim-3) on peripheral T-cells' surface, causing reduces T-cell function and a lack of memory T-cells' activity [9,40]. On the other hand, it has been reported that an elevation in the number of main cells causing cytokine storm (CS), containing monocytes, neutrophils and natural killer (NK) cells is observed in COVID-19 patients [41]. It has been suggested that, changes in the PD-1/PD-L1 pathway in chronic viral infections, like the human immunodeficiency virus (HIV), indicate the rearrangement of monocytes and dendritic cells (DCs) by signal transducer and activator of transcription 3 (STAT3)-dependent IL-10 production in response to the viral infection [42,43]. Moreover, elevated IL-10 levels in COVID-19 patients may also indicate the role of the PD-1/PD-L1 axis in the development of acute viral infections and monocyte rearrangement [44]. Neutrophils of the patients with COVID-19 are not able to regulate the expression of PD-L1 on the surface of immune cells

Table 1
Immunological forecast biomarkers in COVID-19 individuals.

Immunological biomarkers	Immunological effects
NK cell and CD4+, CD8+ counts	The decrease in the numbers of these cells are in accordance with the intensity of the signs in COVID-19 patients [74].
PD-1 and Tim-3 expression on T cells	elevated expression of these two immune checkpoint molecules on T CD4+ and CD8+ cells was found in ICU-hospitalized patients and in non-living patients [40,75].
IL-6	Increased levels of this cytokine were associated with respiratory failure in COVID-19 individuals [76].
IL-10	It was relatively extreme in the patients with severe and critical conditions [77,78].
IFN-γ and IL-2	High levels of their production have been reported in patients with severe acute conditions [79].

compared to a healthy individual, so the levels of PD-L1's expression in these patients is low. Patients with more severe states had greater expressions of PD-L1 on both monocytes and DCs [44]. The examination of the individuals with severe clinical symptoms three weeks after the onset of signs, and elevated expressions of PD-1, perforin and granzyme B in CD4+ or CD8+ cells, showed that the role of T-cells in the progression of the patients' clinical condition is significant [45]. The important point in the treatment of COVID-19 and targeting PD-1 is to adopt a method that can simultaneously reduce and eliminate both the inflammatory cascade and the formation of exhausted T-cells [21]. This goal is achievable through the simultaneous use of anti-PD-1 and anti-interleukin 6 receptor (anti-IL-6R).

3. Cytotoxic T lymphocyte antigen-4 (CTLA-4)

CTLA-4 has been demonstrated to be one of the inhibitory immune checkpoint molecules, although its activity mechanisms are still unknown and may consist several overlapping mechanisms [18]. This molecule functionally inhibits the excitatory activity of CD28 by binding to their common targets such as CD86 and CD80 ligands, that is also involved in the early excitatory stages of immature and memory T cells [18]. CTLA-4 has been revealed to have a great affinity for both of these ligands compared to CD28 when ligand density is limited. This binding is further enhanced by creating network structures using B7 ligand, on the contrary to the monovalent interaction of CD28 with its related ligands [18]. As a result, CD28 is casted out of the immunological synapse by CTLA-4 [18]. This molecule also transmits inhibitory signals to the T-cells and thus inhibits their activation; that eventually leads to the loss of its ligands through their endocytosis on the antigen-presenting cells [46,47]. CTLA-4 is also able to transmit inhibitory signals to ligand-expressing cells by binding B-7 ligands, it also induces inhibitory and suppressive signals in the regulatory or effector T-cells [48,49]. Furthermore, CTLA-4 has major roles in the initial activation of T-cells through dendritic cells (as the main antigen presenting cells). Thus, T cells are activated by the dendritic cells when antigens are present. The beginning of T-cells' activity requires the binding of two cell set, including the *major histocompatibility complex* (MHC)-antigen complex of dendritic cells to T cell receptors as the main stimulus- B7 on the dendritic cells (CD80/86) linking with CD28 attached to T-cells as co-stimulation [50]. CTLA-4 is generally expressed on the surface of T cells and due to its stronger affinity to B7 than CD28, it suppresses the cellular immune responses and impairs T cell functions [51]. Therefore, blocking the pathways associated with CTLA-4 making B-7 available, increases T cells' activity [18]. CTLA-4's have been specifically shown to be expressed on T-cells; while its ligands are expressed on antigen-presenting cells or other immune cells such as T-cells themselves [18].

4. Corona virus deseas-2019 (COVID-19) and immune checkpoints

Sever acute respiratory syndrome coronavirus 2 (SARS-CoV-2) targets cells of the respiratory tract [12,52]. The SARS-Cov2 can also be detected in other organs such as the lungs, pharynx, heart, liver, brain and kidneys; however, the correlation or direct effect of SARS-Cov2 on these organs is still controversial [12]. Studies show that gene expression and the presence of viral genes in respiratory cells are much higher than in kidney, liver, heart, brain and blood cells; which indicates the extensive organotropism of SARS-Cov2 [12]. However, in patients with COVID-19 with both severe and asymptomatic clinical signs, renal tropism and renal impairment have been reported in patients with COVID-19, while there is a debate about the process's underling myocardial injury in this case of patients [12,53,54]. Moreover, Results from autopsy cases, containing positive SARS-CoV-2 in nasopharyngeal swap, showed presence of virus in myocardial tissue with high expression of tumor necrosis growth factors and chemokine ligand 5, as well as IL-6, IL-8, and IL-18 [55]. Therefore, although the hypothesis that the presence of SARS-CoV-2 in addition to the lung can also cause infection in the heart tissue and antiviral immunity plays a role in causing myocardial damage and inflammation [56], but the inflammatory reaction caused by this phenomenon is not a definitive reason for the clinical myocarditis [55]. As mentioned above, owing to the extreme organotropism presence of SARS-CoV-2 in addition to the respiratory tract, this event has been reported to have an effect on the progression of COVID-19 disease and therefore can escalate the disease [12]. Inefficiency of antiviral cell immune parameters, such as the CD8+ T cells, T-reg and monocyte ratio can be a good prognosis for risk of severe cardiac injury [56]. Moreover, suggested that inducing the responses of CD8+ T-cells, but not T CD4+ cells, during the infection of SARS-CoV-2, leads to the simultaneous secretion of Granzyme A, Granzyme B, and perforin from T CD8+ cells [57]. It has also been shown that during acute infections, PD-1 molecules are also expressed on the surface of CD8+ T-cells, but do not lead to their dysfunction [57]. According to a study, the over-expression of PD-1 on the surface of T-cells during primary SARS-CoV-2 infections not only does not impair T-cells, but also it activates them and induces the secretion of perforin and granzymes [57,58]. It has also been shown that in the individuals with COVID-19, the propagation rate of CD4+ and CD8+ T lymphocytes is reduced; as mentioned before, the expression of PD-1 on the surface of T-cells leads to the dysfunction of these cells inhibiting the appropriate immune responses, causes autoimmunity and damages the infected tissues [59]. According to experiments, PD-1's expression, as an important factor in the induction and maintenance of circumferential tolerance keeping the stability of T-cells, has been found to have a higher percentage in different cells of the patients with SARS-CoV-2. Moreover, in the course of PD-1/PD-L1 pathway's activation, inhibitory signals are generated to halter the propagation and the activity of executive T cells; leading to impaired immunity against the virus [59,60]. In an experiment conducted by Diao et al., on the patients with SARS-CoV-2, it was observed that the expression of PD-1 on the surface of T-cells was increased significantly; it was also shown that during the SARS-CoV-2 -induced disease, additional expressions of PD-1 and Tim-3 on the T-cells were directly related to the disease's severity; the factors that were also increased in other viral infections [60]. The expression of PD-1 and Tim-3 factors on the surface of T cells in COVID-19 patients and healthy persons showed that in the COVID-19 infection, there is a T-cells' dysfunction present; and as a result, it requires quick and immediate interventions [40]. It has also been shown that IL-10, as an inhibitory cytokine, prevents T-cells' generation and thus to disrupts and reduces T-cells' activation and proliferation, leading to the dysfunction of cellular immune responses [40]. SARS-CoV-2 in addition to direct cytotoxicity, can lead to tissue damage by activating cytokine cascades in the host [9]. Besides, the overexpression of PD-L1 as well as the proinflammatory cytokines, such as IL-6, IL-1 and TNF-α, has been reported in monocytes and DCs. In addition, along the SARS-CoV-2-induced viral infection, signal transducer and activator of transcription 3 (STAT-3)-induced IL-10 secretion, leads to the overexpression of PD-1 and PD-L1 in monocytes and DCs [9]. Monocytes involved in COVID-19, similar to the monocytes involved in hepatitis C infection, have been reported to over expressions of PD-L1 and IL-10, and down expressions of Human Leukocyte Antigen – DR isotype (HLA-DR) and CD86 [61]. In addition, it has been observed that in the COVID-19 disease, unlike monocytes and DCs, neutrophils express less PD-L1; In contrast, they are characterized by the significant secretion of proinflammatory cytokines induced by ss-RNAs [62]. Correspondingly, neutrophils are more abundant in the peripheral blood during the course of COVID-19, given their weaker ability to secrete cytokines than monocytes and DCs [62] (Fig. 1).

5. Conclusion

The examination of clinical specimens obtained from the patients with severe signs of COVID-19 can show the role of immunological

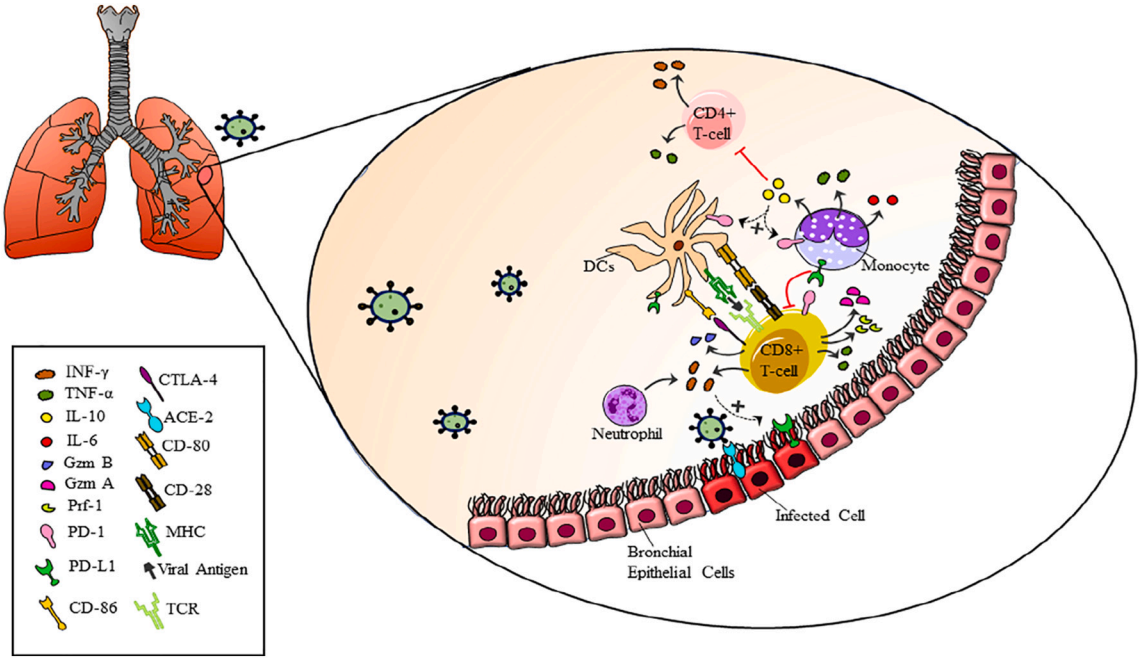

Fig. 1. The roles of PD-1 and CTLA-4 axis in the regulation of immune cells during respiratory viral infection.

factors leading to severe conditions. Modifying these immune inhibitory agents and suggesting their related medications can provide ways to improve its symptoms and even treat or immunize the SARS-CoV-2 virus. The elevation in the count of lymphocytes, especially T-cells, in COVID-19 patients indicates the importance of acquired cellular immunity in the course of pathogenesis, immunity and the exacerbation of COVID-19 in subsequent periods of infection. Studies show the importance of cytotoxic CD8 + T-cells in controlling primary SARS-CoV-2 infections. In other words, the increase of cytokines such as IL-10, IL-6 and TNF-α in these patients and their role in reducing T-cells worsens the disease's condition [62]. New therapies for the cure of COVID-19 patients could be fundamental approaches such as targeting the pathways of immunosuppressive adjusting molecules like Tim-3, PD-1, increasing cellular immune functions by increasing T-cell and NK cell counts, and functions, not only in the treatment of cancer, but also, in the face of respiratory infections [38,63]. Given the role of IL-10 along with Tim-3, appearing as markers of T-cells' exhaustion, it can be expected that blocking IL-10's function is effective in preventing T-cells' exhaustion and increasing its function in chronic infections [62]. Considering the similarities between the symptoms of the deadly H7N9 disease to COVID-19 patients, caused by high levels of cytotoxic granules that may be associated with defective activation and the exhaustion of T-cells; it can be expected that medications with immune checkpoint inhibitors, when administered to COVID-19 patients, can possibly end this dire situation and even reverse it [64,65]. Given the essential and distinct roles that CTLA-4 and PD-1 have in regulating T-cells' activities, blocking their pathway can be synergistic, meaning that CD8+ T-cells responses to these biomarkers can effectively alter T-cell activity, but can also potentially cause high toxicity of them [66].

Evaluation of serum factors in the individuals with severe COVID-19 signs indicates the development of cytokine cascades caused by the overactive innate immune system [67,68]. In addition, the decreased count of T-cells and the increased expression of PD-1 and Tim-3, indicate T-cell exhaustion and dysfunction in the adaptive cellular immune system, enable to remove the infection [40]. Therefore, it seems that the use of ICI may be effective in curing COVID-19 and reactivating the exhausted T-cells. However, according to previous studies, the possibility of a cytokine cascade caused by ICI should not be ignored as the use of ICI for more than 90 days in the individuals with cancer increased the severity of COVID-19 symptoms [69]. However, in another study, there was no correlation between ICI administration and the intensity of COVID-19 [70]. Therefore, the effects of ICI on COVID-19 should be studied extensively and comprehensively. All of these studies introduce ICIs as drugs that increases the immune system's activity and in addition to their therapeutic use for cancer, are able to increase the function of the suppressed immune system through increasing the response of T-cells to antigens and viruses in cases such as sepsis and influenza infections [71]. Studies show that empowering the T-cells' immune responses by blocking PD-1/PD-L1 and CTLA-4 through specific antibodies is effective in improving the disease's course, obliterating the pathogens and enhancing the survival of septic patients and immunodeficiency patients [72,73]. The expression of PD-L1, impelled by the interferons secreted by T-cells on the surface of tumor cells and its binding to PD-1, leads to the inhibition of T-cells' function. It has also been revealed that the inhibition of T lymphocytes' function is due to the cooperation of CTLA-4 and B7. As a result, by targeting the PD-1/PD-L1 and CTLA-4/B7 pathways, the activity of T-cells is increased leading to the identification of the tumor through the immune mechanisms. To sum up, the PD-1/PD-L1 and CTLA-4/B7 pathways play a crucial role in COVID-19 infection, warranted to raise concerns to combat better with this viral infection.

The infection of the target cells by SARS-CoV-2, start the activation of innate and acquired immune system cells; including T cells and DCs. These immune cells secrete inflammatory cytokines such as, IL-10 and INF-γ. IL-10 in turn, increases the expression of PD-1 on the surface of monocytes and DCs and suppresses CD4+ T-cells' functions and differentiation. Also, followed by the presentation of antigens by DCs to the CD8+ T-cell, CTLA-4 binds to its ligand (CD-86) which is expressed on the surface of DCs, and consequently, suppresses the activity of the CD8+ T-cells. Likewise, the attachment of monocytes' PD-L1 to the PD-1 expressed on the surface of CD8+ T-cells also inhibits their antiviral activity and ultimately conducting to the disease progression.

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