Immunol Genet J, Vol. 7, No. 3, September 2024, pp.95-98 DOI: https://doi.org/10.18502/igj.v7i3.17876

Review Article

The Role of Cytotoxic T-Cells in COVID-19: Potential Therapeutic Targeting

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Received: 26 April 2024; Accepted: 5 August 2024

Abstract

A novel coronavirus disease (COVID-19) have raised in Whuan in December 2019. This disease kept spreading rapidly until World Health Organization have declared a pandemic on COVID-19. Despite all the efforts made there are no definite treatments for this disease. Recent papers on pathophysiology of COVID-19 have shown possible mechanism of T-Cell exhaustion caused by virus is responsible for lymphopenia observed in these patients. PD-1/PD-L1 have a major role in T-Cell exhaustion so we have proposed targeting PD-1/PD-L1 using anti-PD-1/PD-L1 agent. Using anti-PD-1/PD-L1 agents including Pembrolizumab and Nivolumab could potentially decrease T-Cell exhaustion and increases survival of COVID-19 patients. In order to overcome the shortcoming of this approach we have proposed using clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) which can be highly efficient in targeting PD-1/PD-L1. Using CRISPR/Cas9 in this regard could be more efficient, feasible and economical and potentially lower side effects. In conclusion targeting PD-1/PD-L1 through approved medications or CRISPR/Cas9, in order to block their interactions, may remarkably prevent the cytotoxic lymphocytes functional exhaustion, especially CD8+ T-cells and help to decrease the mortality rate in COVID-19 patients. In addition, to evaluate the clinical outcome of using anti-PD-1/PD-L1 agents or CRISPR/Cas9 system in COVID-19 patients, it is recommended to measure lymphocyte, CD8+ T-cells, NK cells and total T-cells count.

Keywords: COVID-19; PD-1; PD-L1; Anti-PD-1/PD-L1; CRISPR

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How to cite this article
Hessami A, Heydari K, Hosseini A, Asgari N. The Role of Cytotoxic T-Cells in COVID-19: Potential Therapeutic Targeting. Immunology and Genetics Journal, 2024; 7(3):95-98. DOI: https://doi.org/10.18502/igj.v7i3.17876

Introduction

A novel coronavirus disease (COVID-19) was developed in Wuhan, China, in December 2019. The new virus, which is also called respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread rapidly throughout the world and was declared a pandemic by the World Health Organization (WHO) on March 11, 2020 (1). Although it has been several months since the onset of the outbreak, there is still no specific preventive and

therapeutic approach against SARS-CoV-2.

T Cell exhaustion

Studies on previous similar pathogens of the same family, SARS-CoV, showed that infection in severe cases was associated with delayed adaptive immune responses and viral clearance. (2). High viral load was associated with the severity of the disease and can be affected by the immune system. (3). Besides, this acute phase is also associated with a high reduction of blood T-cells. Although T-cells mediated adaptive immune response has not been studied much regarding the pathogenesis of respiratory coronavirus, a cohort study by Cui et al. has reported interesting findings in this regard as follows: leukopenia, T-cell lymphocytopenia, and total lymphopenia were observed in 47%, 95%, and 84% of SARS patients, respectively. Also, levels of CD4+ and CD8+ T lymphocytes were reduced in 100% and 87% of patients, respectively, as well as a 76% reduction in B lymphocyte levels and a 55% reduction in Natural killer (NK) cells (4).

A decreased number of T lymphocytes was correlated with the severity of the disease; however, the direct infection of T-cells by SARS-CoV is not well-known yet; it has been discussed that changes in antigen-presenting cells (APCs) and Dendritic cells (DCs) might contribute to the low number of T-cells (2). Hence, NK cells and cytotoxic T lymphocytes (CTLs) seem to be the most important defensive factors against viral infections. Decreasing these cytotoxic lymphocytes may lead to the development of the infection, which is known as functional exhaustion(5). Although this had not been discussed in SARS-CoV-2, Zheng et al. recently studied the "functional exhaustion of antiviral lymphocytes in COVID-19 patients." (6). This study indicated a significantly decreased number of NK cells and CD8+ T cells in COVID-19 patients, induced by increased expression of CD94/NKG2A inhibitory receptor, a cell surface molecule expressed on NK and CD8+ T cells. Cytotoxic lymphocytes are functionally exhausted through CD94/NKG2A upregulation, which has also been reported in previous studies regarding malignancies and chronic infections(7, 8). Hence, normalizing the lymphocyte counts might improve clinical condition of same disease to COVID-19, caused by a family member of coronaviruses (9) and preventing cytotoxic lymphocytes functional exhaustion through immune checkpoint blockage in early stages of infection with SARS-CoV-2 can substantially help to virus elimination. One of the most studied and better-known immune checkpoints is Programmed cell Death protein 1 (PD-1) and its ligand (PD-L1), which can be targeted with anti-PD-1 and anti-PD-L1, Food and Drug Administration (FDA) approved medications

PD-1/PD-L1 role in exhaustion

PD-1 is an immune receptor with a wide range of distribution in immune responses, including autoimmunity, infectious immunity and tumor immunity (10). This receptor is being expressed on T-cells and when it binds to PD-L1, it will decrease the T-Cell proliferation (11). PD-1 expressed as a natural response of T-cell activation in order to avoid hyper immune responses and terminate the immune reaction (12). Tumor cells expressing PD-L1 will induce apoptosis of T-cells and make them escape from the immune system. Thus, targeting PD-1/PD-L1 is an option for cancer therapy (13). Furthermore, the role of PD-1/PD-L1 in T-cell exhaustion has been previously demonstrated, especially during viral infections (14-16).

PD-L/PD-L1 as potential targets for COVID-19

According to previous studies, PD-1 blockage in viral infections resulted in considerable viral control and a reduction of mortality rate (15). There is only one study regarding COVID-19 on "functional exhaustion of antiviral lymphocytes" by Zheng et al.; the study indicated that lymphocytopenia due to COVID-19 has probably originated from T-cell exhaustion since the number of T-Cells were significantly lower in severe cases in compare to healthy population and mild cases, which has been reinvigorated in convalescent patients (6). With regards to PD-1 role in T-cell exhaustion that seems to be the cause of lymphocytopenia in COVID-19 patients with poor outcome, we hypothesize that using anti-PD-1/PD-L1 agents could also prevent the T-cell functional exhaustion and help to increase the survival rate. However, regardless of the feasibility, the approach might cost a lot and its potential side

effects should also be considered.

Anti-PD-L/PD-L1 agents

Pembrolizumab and Nivolumab as humanized antibodies are anti-PD-1 FDA-approved medications clinically well-developed for targeted immunotherapy (17). Moreover, fully human monoclonal FDA-approved antibodies, Atezolizumab, Durvalumab, and Avelumab as anti-PD-L1 agents blocks the interaction of PD-L1 with the PD-1 in cancer therapy purposes (18). Meanwhile, several adverse effects have been reported for PD-1/PD-L1 blockade agents, including pruritis, fatigue, loss of appetite, dermatitis, hypophysis and colitis, which are generally managed by corticosteroid parallel treatment (17).

CRISPR/Cas9; Economical, Feasible, Few Side Effects

To overcome the shortcomings of the former approach, we can turn to a new therapeutic strategy in targeting PD-1/PD-L1, using clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9), as an RNA-guided DNA endonuclease, which can be highly efficient in this regard. As studies by Yunfei et al. (19) and Yahat et al. (20), successfully showed that PD-L1 expression could be disrupted by CRISPR/Cas9 system following T-cells increase both in vitro (osteoblastoma) and in vivo (ovarian cancer). This gene-editing technology was appeared to be safe and feasible in clinical trial on three refractory cancer patients (21). This tool has also demonstrated promising outcomes for Epstein-Barr virus (EBV)-associated gastric cancer in a xenogenic mouse model (22).

Considering recent in vitro and in vivo studies on mechanisms of CRISPR/Cas9 and pathophysiology of COVID-19, CRISPR/Cas9 system could be applied to improve the outcome of patients with COVID-19 through knock out of PD-1/PD-L1. This new approach costs reasonably following few potential unintended side effects. However, further studies are needed to evaluate its efficacy and safety against COVID-19.

Conclusion

According to all the mentioned above-mentioned facts, targeting PD-1/PD-L1 through approved medications or CRISPR/Cas9, in order to block their interactions, may remarkably prevent the cytotoxic lymphocytes functional exhaustion, especially CD8+ T-cells and help to decrease the mortality rate in COVID-19 patients. In addition, to evaluate the clinical outcome of using anti-PD-1/PD-L1 agents or CRISPR/Cas9 system in COVID-19 patients, it is recommended to measure lymphocyte, CD8+ T-cells, NK cells and total T-cells count.

Conflicts of interest

The authors declare no conflicts of interest.

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