Latest updates on SARS-CoV-2 (Corona Virus)

Chapter 4

Characterization of the Interaction between COVID-19 and Cancer in Comorbid Patients

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Abstract

The spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused great economic losses and life threats. Concomitantly, cancer overtakes cardiovascular disease to become leading cause of death. The effects and mechanisms of their interaction are rarely comprehensively summarized when a sudden disease (COVID-19) collides with an incurable disease (cancer), which has existed for a long time. Here, we'll discuss the interaction between the COVID-19 and cancer in comorbid patients, and the full-scale understanding may better promote the clinical treatment of COVID-19 patients with concomitant cancer.

Keyword: SARS-CoV-2; COVID-19; Cancer; Cytokines; Immune cells; Hypoxia; Conventional treatment.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a positive-strand RNA virus that caused the sudden disease known as COVID-19. The current number of patients with COVID-19 is still escalating. As of July 9, 2021, 185,038,806 cases have been

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confirmed as COVID-19 patients in worldwide, among them, 4,006,882 patients were dead, and the numbers are increasing dramatically every day (https://covid19.who.int/). It is well known that the respiratory system and immune system are the first to be attacked by the virus, and then other systems, including blood circulation system, urinary system and reproductive system, are also attacked, because most likely angiotensin-converting enzyme 2 (ACE2), as a binding receptor of spike protein on SARS-CoV-2, is highly expressed not only in respiratory tract epithelial cells, but also in vascular endothelial cells [1], kidney and testis [2]. Thus, there are two ways for patients with cancer to be affected by SARS-CoV-2 infection: one is the direct way that SARS-CoV-2 damages the specific organ's function, and then the tumor in this area is affected; the other is the indirect way that the affected immune system and blood circulation system change the tumor microenvironment, resulting in the promotion or inhibition of tumor growth.

Cancer is a large group of diseases which can occur on almost any tissue or organ of the body, characterized by the uncontrolled growth of some cells in the tissue or organ [3]. In patients with cancer, the state of immunity is usually severely suppressive [4]. Thus, this makes cancer patients more susceptible to SARS-CoV-2 infection. In this review, we will discuss in detail the interaction between tumor and SARS-CoV-2, and the potential mechanism of action.

2. Effect and Mechanism of SARS-CoV-2 onTumor

After SARS-CoV-2 infection, the patients have a high risk of pneumonia and hyperinflammation, and even pulmonary fibrosis. Activated hyperinflammation response, also known as cytokine storm, increases the levels of pro- and anti-inflammatory cytokines in blood and other tissues, including IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9 and IL-10 [5-7]. Among them, IL-1, IL-4, IL-5, IL-6, IL-8 and IL-10 promote tumor development [8-13], the others of IL-2, IL-7 and IL-9 repress tumor development [14-16]. Interestingly, type-I interferon (IFN) cytokines, such as IFN-α, and the type-II IFN cytokines, such as IFN-γ, are both expressed increasingly in COVID-19 patients [17], and type-I IFNs can further activate type-II IFNs [18]. Both of them show anti-tumor effect by directly inhibiting tumor or indirectly promoting immune response [19, 20] (Fig. 1A). Consistent with the above, a special cancer case with Hodgkin lymphoma was cured after SARS-CoV-2 infection, and the underlying mechanism is presumed to be an inflammatory response triggered by SARS-CoV-2 [21].

Immune cells are important components in immune system to clear virus and prevent disease. In acute SARS-CoV-2 infection, natural killer (NK) cells were decreased in cell numbers in peripheral blood and maintained their exhausted phenotype [22]. These weaken the anti-tumor response of NK cells. In addition, the amount of monocytes and dendritic cells also were lower in COVID-19 patients than in healthy donors, and even the functions of DCs were damaged by SARS-CoV-2 [23], which directly impaired the acquired immune response.

More unexpected, T-cell lymphopenia was observed in COVID-19 patients, resulting from the blocking of T cell proliferation and IL-2 production [24]. Conversely, PD-1, a marker of T-cell exhaustion, was expressed higher in CD4 T cells of COVID-19 patients than healthy donors, indicating possible exhaustion of CD4 T cells [24]. These cells were most likely further inhibited by tumor cells through the PD-L1/PD-1 signaling [25]. In COVID-19 patients, some immune cell counts are elevated in the blood. Indeed, several studies had shown that the increased neutrophil counts in the blood have been as a feature of COVID-19 in the clinics [26, 27], and neutrophil activation was also present in patients with COVID-19 [28]. Other studies reported that macrophages are increased in number [29] and activated [30] after SARS-CoV-2 infection. Unfortunately, tumor-infiltrating neutrophils and macrophages both stimulated tumor progression by enhancing Oncostatin M (a pleiotropic cytokine of IL-6 family)-mediated angiogenesis and metastasis [31]. Thus, SARS-CoV-2 may contribute to development of tumor by regulating the number and function of those immune cells.

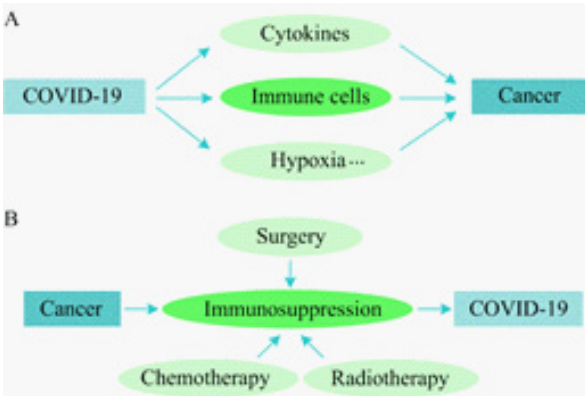

Figure 1: Influence of the interaction between COVID-19 and cancer. (A) COVID-19 alters tumor progression through multiple pathways, including secreting cytokines, immune cell status, hypoxic conditions and so on. (B) Cancer promotes the susceptibility of SARS-CoV-2, and the active treatment for tumor further aggravates the effect.

Lung disease was induced by SARS-CoV-2, characterized by damaged airway epithelium, occasional hyaline membrane formation, pulmonary edema [32], CT pulmonary angiography, and even pulmonary fibrosis, which cause chronic dyspnea [33]. Thus, the injury of lung tissue can lead to systemic hypoxia, which can induce a hypoxia-associated resistance in cancer therapy via HIF 1α-related signaling on tumor microenvironment [34]. Therefore, oxygen supply to COVID-19 patients is also beneficial to the treatment of tumor. The fibrosis in the lung is mainly contributed by TGF-β [35], which could promote tumor progression in a multi-pathway manner [36, 37]. In this regard, SARS-CoV-2-induced TGF-β is not only beneficial to the development of pulmonary fibrosis, but also promotes the tumor progress. Taken overall, SARS-CoV-2 may alter tumor progression through secreting cytokines, immune cell status and hypoxic conditions.

3. Effect and Mechanism of Tumor on SARS-Cov-2

Cancer patients have a suppressed immune response, which allow tumor cells to escape immune surveillance. Especially, the body's immunity will be further suppressed after

conventional cancer treatment, including surgery [38], radiotherapy [39], and chemotherapy [40]. As a result, cancer patients are more likely to be infected with SARS-CoV-2 in the case of external exposure. In line with these observations, a separate investigation reported that, among 1276 confirmed cases in Wuhan, there are 28 cancer patients [41], and the incidence rate is 2.5%, which is much higher than that incidence rate (0.29%) of 2015 cancer epidemiology statistics [42].

A meta-analysis of 17 studies involving 4635 subjects showed that tumor was significantly associated with severe events of COVID-19 [43]. Among patients with cancer, several studies had showed that the severe cases are mainly caused by older age, as a high risk factor [44-46]. To be specific, Vikas Mehta and colleagues' research showed that the median age of patients who died of COVID-19 was 76 years, and the age was 10 years older than those who were still alive [45].

As mentioned above, the risk of infection increased in patients with antitumor therapy because of further immunosuppression. COVID-19 patients who underwent surgery had a higher rate of respiratory support than those who did not receive any antitumor therapy, and presented a similar rate of ICU admission and mortality in patients without receiving tumor surgery [47]. However, if the cancer patients received radiotherapy or chemotherapy in a certain time before the COVID-19 diagnosis, the patients were at higher risk of developing severe events and death [41, 45, 47]. Similarly, patients who have received cancer immunotherapy and targeted therapy also have these characteristics [41]. Thus, during the COVID-19 pandemic, the routine treatment for cancer patients was affected, a collaborative approach to treat cancer and COVID-19 may need to be developed.

4. Conclusions and Perspectives

Currently, the characterization of interaction between COVID-19 and cancer is further discussed in comorbid patients. COVID-19 affects the progression of cancer, which in turn promotes the susceptibility of SARS-CoV-2. This requires cancer patients and COVID-19 patients to strictly live separately to avoid cross infection, and optimizing cancer and COVID-19 care. Although an individual case has reported that the COVID-19 cured tumors, the mechanism is not fully elucidated. This finding highlights the importance of researchers to face the difficulties and continue to uncover more truth behind the COVID-19. Additionally, more intensive surveillance, earlier identification and extensive treatments should be considered when cancer patients are infected with SARS-CoV-2, especially in elderly patients or other comorbid patients.

5. Competing Interests

The authors declare that they have no competing interests.

6. Acknowledgments

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