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Review Article

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SARS-CoV-2 Infection: A Possible Risk Factor for Incidence and Recurrence of Cancers

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ABSTRACT

COVID-19 and malignancy can affect the susceptibility of one another. Clinically recovered COVID-19 individuals display immune abnormalities that persist several months after discharge. The lymphopenia-related immunosuppression, functional exhaustion of cytotoxic lymphocytes (such as $CD8^+$ cytotoxic T-cells and natural killer cells), hyperinflammatory responses, oxidative stress, downregulation of interferon response, development of the myeloid-derived suppressor cells, downregulation of tumor suppressor proteins and perhaps reactivation of the latent oncogenic viruses may directly and/or indirectly play a role in the cancer development and recurrence in severe COVID-19 patients. SARS-CoV-2-infected malignant patients may be at higher risk of death of their cancer than SARS-CoV-2-uninfected patients with the same cancers. On the other side, the patients with some types of cancers may be more vulnerable to SARS-CoV-2 infection compared with the non-cancerous individuals, due to their immunocompromised state resulted from malignancy, chemotherapy, and other concomitant abnormalities as well as perhaps greater expression of angiotensin-converting enzyme 2. SARS-CoV-2-infected cancerous patients are unable to produce an effective anti-virus immune response and may exhibit more severe forms of COVID-19. This review described the possible impacts of SARS-CoV-2 infection on cancer development and recurrence, and the potential cancer impacts on COVID-19 development, while the possible interventions are highlighted.

Keywords: COVID-19; Cancer; SARS-CoV-2; Immunosuppression; Inflammation; Oncology; Malignancy

INTRODUCTION

The SARS-CoV-2-mediated coronavirus disease 2019 (COVID-19) pandemic has affected a great number of populations in about 200 countries and territories[1]. SARS-CoV-2 is transmitted predominantly by symptomatic, pre-symptomatic, and asymptomatic carriers, mainly via respiratory droplets during face-to-face exposure such as coughing, talking, and sneezing. Aerosols and to a smaller extent, infected surfaces may also spread the virus [2].

Patients with underlying disorders, including diabetes, hypertension, cancer, chronic respiratory disease, and cardiovascular diseases are more vulnerable to COVID-19 [3]. The elderly individuals and those with impaired immune system are at a greater risk of developing serious and even deadly respiratory disorders[3]. The COVID-19-related symptoms appear after an incubation time with a median of approximately 5 days [4,5]. The period from the initiation of COVID-19 signs to possible dying differs from 6 to 41 days with an average of 14 days [4,5]. It was estimated that approximately 10.0% of patients with COVID-19 experience prolonged manifestations (for over 3 weeks) and in 1.5%-2.0% of patients, signs persist for over 90 days [6,7]. Some cases have been considered as chronic COVID-19 when symptoms extending beyond 12 weeks [6]. Long COVID19 can be the result of low grades of the virus being sequestered in certain tissues, making it impossible to be identified by conventional diagnostic tests [8]. In the patients with long COVID-19, the virus can exert profound modulatory effects on the immune system and induce low-grade chronic inflammatory responses[8,9]. Thus, SARS-CoV-2 infection, especially in its long term, can act as a risk factor in cancer development.

Data reported from Wuhan, China showed that about 1.0-2.0% of COVID-19 patients were diagnosed with malignancy [10,11]. However, about 6.0% of hospitalized subjects with COVID-19 from New York City had cancer [12], and about 8.0% of COVID-19 patients who needed the ICU facilities had an active or early history of malignancy [13]. In another study from Italy, about 20.0% of the COVID-19-related deaths occurred in patients with active malignancy [14].

The immune system performs an essential role in defending against tumor cells. As a result, the occurrence of malignancy is significantly higher in immune-compromised hosts [15]. Based on immune surveillance concepts, an essential duty of the immune system is to carefully examine the development of malignancy in the body and eliminate tumor cells as they emerge [16]. In the immune system, the Th1 cells show potent anti-tumorigenic effects via recruitment of the natural killer (NK) cells, M1 type macrophages, and $CD8^+$ cytotoxic T lymphocytes (CTLs)[17,18]. Conversely, type 2 macrophages (M2), myeloid-derived suppressor cells (MDSCs), Th2 cells, and regulatory T (Treg) cells inhibit the anti-tumor immune responses [18,19]. Tumor cells also escape immune-mediated recognition/elimination by a number of mechanisms, particularly down-regulating of anti-tumoral immune responses [20]. Clinically recovered COVID-19 individuals display profound immunologic alterations in both innate and adaptive immunity compartments that persist several months after discharge [21-23]. Anti-tumor immune responses can be weakened because of these immunologic changes.

The malignant patients exhibit a greater risk of SARS-CoV-2 infection. The results from a study conducted in Spain indicated that 31.4% of the cancer patients were seropositive for specific IgG or IgM against SARS-CoV-2, while seropositivity in the general population was 10.0% [24]. In the general population, the fatality rate of COVID-19 is estimated to range from 2 to 3%. However, cancer patients are more susceptible to COVID-19 and have a 25.0%-39.0% mortality risk if infected with SARS-CoV-2 [25]. Thus, COVID-19 and malignancy can influence each other susceptibility. SARS-CoV-2 infection may profoundly attenuate the anti-tumoral immune responses. Therefore, the COVID-19 patients may be immunocompromised to an extent where the anti-tumor response is depleted causing cancer development and cancer recurrence. This review explains the possible SARS-CoV-2-mediated impacts on the development of cancer and cancer recurrence, and the potential cancer impacts on the COVID-19, while the possible interventions are highlighted.

Pathophysiology of COVID-19

Four main structural proteins of coronaviruses include spike (S), nucleocapsid (N), envelope (E), and membrane (M), among which S protein plays a fundamental role in the virus binding to its cell receptor, angiotensin-converting enzyme-2 (ACE2) [1,26]. Upon respiratory infection with SARS-CoV-2, an initial proper IFN response (primarily type III IFNs) effectively eliminate the virus without the expression of the clinical symptoms or with the expression of mild signs [27]. If the patient is

immunocompromised or if the initial IFN response fails, the virus expands, then enters the bloodstream from the lungs and infects ACE2 expressing organs [27]. The tissues and cells that express ACE2 are considered as the possible target of SARS-CoV-2. The greatest expression of ACE2 has been recorded in the gastrointestinal tract, testis, and kidneys [28]. In the lungs, ACE2 is highly expressed by type II alveolar cells, and in the liver, ACE2 expression was observed in cholangiocytes [1,28]. The enterocytes of the small intestine express more ACE2 compared with those from colon regions [28]. ACE2 is also expressed by stratified epithelial cells of the esophagus, proximal tubule cells of kidney, and urothelial cells of the bladder[1,26,29]. ACE2 expression has also been documented in CNS blood vessels that provide a direct route for SARS-CoV-2 entry into the brain [28,30]. Coronaviruses can also attack the peripheral nerves, and then reach the CNS via the synaptic pathway [31]. Collectively, the massive virus replication, viral-mediated ACE2 downregulation, immune dysfunction, over-inflammatory reactions, cytokine storm, lymphopenia, enormous cell death (in particular endothelial- and epithelial cells) through apoptosis, necrosis and pyroptosis, coagulopathy, vascular leaks, and lung fibrosis can play prominent roles in the COVID-19 pathogenesis[32,33]. The anti-virus IFN response is impaired in severe COVID-19 patients, however, these patients experience a destructive cytokine storm which is characterized by a dangerous increase in the circulatory quantities of cytokines such as IL-6, TNF-α, IL-1β, IL-2, IL-7, IL-8, MIP-1α, CCL2 and CXCL10 (IP-10) [4,27]. Cytokine storm can promote viral sepsis and contributes to coagulopathy, vascular leak, multiple organ failure, in particular, acute respiratory distress syndrome (ARDS) [4,27].

In the lung-related innate immunity, viral-derived RNAs are sensed by toll-like receptors (such as TLR7 and TLR8) and cytoplasmic sensors [such as retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated protein 5 (MDA-5)] leading to the IFN production [27]. However, SARS-CoV-2 can effectively downregulate anti-virus IFN response [34,35]. Moreover, a number of SARS-CoV-2-derived molecules activate NLRP3 inflammasome resulting in the pyroptosis and releasing of IL-1β and IL-18 which promote HMGB1 release, Th17 cell activation, neutrophil recruitment, macrophage activation and cytokine storm [36].

Direct interaction between SARS-CoV-2 with platelets, virus-induced complement activation and microvascular damage over-activate platelets which can lead to thrombosis [37]. Among inflammatory markers, IL-6 and CRP support thrombosis state [33,37]. Diverse cytokines have been implicated in the process of lung fibrosis such as TGF-β and IL-6 [38]. During COVID-19, TGF-β is produced by various types of cells such as platelets, macrophages and infected type 2 alveolar cells [33]. TGF-β exerts fibrogenic activity via inducing the proliferation and migration of fibroblasts and stimulating the formation of the extracellular matrix [33,38]. Local IL-6 overexpression also exacerbated fibrosis through the promotion of the pro-fibrotic activity of M2 macrophages [33]. IL-6-dependent signaling in the vascular epithelial cells lead to up-regulation of the VEGF and downregulation of the E-cadherin promoting vascular permeability and leakage [33].

COVID-19 patients, in particular, those with severe forms of illness have lower blood numbers of $CD3^+$ T lymphocytes, B lymphocytes, $CD4^+$ T cells, $CD8^+$ T cells, and NK cells [39]. The results from different studies indicate that approximately 33.0%–96.0% of patients with the severe form of COVID-19 display lymphopenia which has a close relationship with illness progression and fatality rate [39]. Lymphopenia can lead to immune depression and promote cytokine storm, both of which play important roles in virus dissemination and multi-organ failure [33,39]. Moreover, total lymphocyte counts are significantly decreased in COVID-19 patients > 50 years old than those < 50 [40].

Additionally, a small subset of monocytes, macrophages and T cells may also be infected by SARS-CoV-2 via ACE2-dependent and ACE2-independent process using L-SIGN, DC-SIGN, CD147, antibody-dependent enhancement (ADE), and perhaps phagocytosis of apoptotic bodies containing the virus [32,41-44]. The infection of some types of leukocytes by SARS-CoV-2 can compromise the innate and adaptive immune responses. SARS-CoV-2 can effectively suppress the anti-viral interferon (IFN) response in antigen presenting cells (APCs)

such as monocytes and macrophages and dendritic cells (DCs) [4,45].

In convalescent patients, the functional abnormalities of the T and B cells also persist up to 6 months after discharging from hospital [22]. Yang *et al*. also indicated that the clinically recovered COVID-19 individuals display immune abnormalities such as lower circulatory numbers of Th1-, Th2-, Th17-, Tfh-, memory B-, and central memory T cells within 4-11 weeks after discharge [21]. Kostopoulos et al. also indicated that some immunologic alterations such as reduction of circulatory B cells persist up to eight months after SARS-CoV-2 infection [23]. Therefore, SARS-CoV-2 infection-related immune abnormalities, especially in its long term can disrupt the anti-tumoral immune responses.

Risk of tumor development can be enhanced after SARS-CoV-2 infection

1) Anti-tumoral immune responses are compromised after SARS-CoV-2 infection

In the immune system, NK cells are the first line of protection against tumor- and virus-infected cells [46]. Positivity for the CD16 and CD56 expression is among the most important of NK cell features [47]. The NK cell activity is controlled by a number of activating and inhibitory receptors. The NK cell-mediated elimination of the target cells depends on the balance between activating and inhibitory receptors, causing the NK cell to discriminate normal cells from unwanted cells [48]. In the adaptive immunity, the $CD8^+$ T cells kill cancerous- and viral-infected cells following the identification of the tumor- and viral-related antigenic peptides bound to MHC class I molecules expressed by target cells. $CD4^+$ T cells provide the necessary signals for activating of the $CD8^+$ T cells, which are then differentiated to effector CTLs that kill target cells via release of granules or by FasL-mediated apoptosis [49].

The number of $CD16^+$ $CD56^+$ NK cells are markedly diminished in severe COVID-19 than in mild cases and healthy people [50-52]. In the severe COVID-19 patients, the total counts of $CD4^+$ T and $CD8^+$ T cells are also reduced compared with other patients, which indicate that COVID-19 can exert profound impacts on lymphocyte [40,50-52].

The reduced numbers of $CD56^{dim}$ NK cells (a subset of NK cells with cytotoxicity activity), and the reduced levels of NK cell-activating cytokines (including IL-12, IL-15, and IL-21) were indicated in the severe COVID-19 patients [53]. The overexpression of an inhibitory receptor, called NK group 2 member A (NKG2A), occurs by $CD8^+$ T- and NK cells from COVID-19 patients in comparison to healthy people [51,54,55]. Lower counts of NK and $CD8^+$ T cells expressing CD107a (an activation marker), IFN-γ, and IL-2, were detected in COVID-19 patients in comparison with healthy controls [51]. The intensity of granzyme B expression was also diminished in the NK and $CD8^+$ T cells from COVID-19 patients compared with healthy individuals [51]. The percentages of the TNF-α^+ NK-cells were also diminished in COVID-19 patients [51]. The overexpression of NKG2A on CTLs and NK cells from COVID-19 patients is associated with the small expression of IFN-γ, IL-2, TNF-α, CD107a, and granzyme B [51]. Thereby, the overexpression of NKG2A leads to the functional exhaustion of $CD8^+$ T and NK cells in COVID-19 patients compromising immune responses against the cancers and viral pathogens [51,54,55]. In convalescent COVID-19 patients, the functional abnormalities of the $CD8^+$ T cells persist up to 6 months after discharge from the hospital [22].

The NKG2A overexpression and next exhaustion of T lymphocytes and NK cells occur in some types of cancer displaying tumor growth [54,56]. The binding of NKG2A to its relevant ligands prevents $CD8^+$ T and NK cell-mediated activities, whereas NKG2A blocking on CTLs and NK cells diminishes tumor growth through improving the $CD8^+$ T- and NK cell-mediated activities [54,57]. Therefore, it is important to improve the NK cells and CTL-related activity and avoid their exhaustion to prevent the damping of anti-tumor immunity during SARS-CoV-2 infection. The targeting of NKG2A may repress the NK cell and CTL exhaustion and thus cause virus clearance in the initial step of SRAS-CoV-2 infection [51]. Monalizumab, an anti-NKG2A monoclonal antibody, improves the $CD8^+$ CTL and NK cell-mediated responses in cancers and successfully prevents the progression of tumors with no major harmful impacts in phase 2 clinical trials [57,58]. COVID-19 patients also have greater plasma quantities of IL-6 and TNF-α which may

impair the NK cell activity, thus the targeting of TNF-α and IL-6 can improve the NK cell activity in COVID-19 patients [28].

It should also be noted that $CD4^+$ T lymphocytes play a central role in the induction of anti-tumoral and anti-viral immunity. $CD4^+$ T lymphocytes recognize antigenic peptides associated with the MHC class II molecules on the membrane of APCs and provide aid for NK cells and $CD8^+$ CTLs to exert anti-tumoral and anti-viral effects. The marked reduction of the MHC II molecules expression on $CD14^+$ monocytes was also reported in severe cases of COVID-19, which has been associated with profound depletion of $CD4^+$ T- and NK cells [52]. The low expression of MHC II molecules on $CD14^+$ monocytes has been attributed to the IL-6 and *in vitro* experiments using tocilizumab prevent the reduction of the expression of MHC II molecules by monocytes incubated with plasma samples collected from immunocompromised COVID-19 patients [52].

Collectively, the results from aforesaid studies clearly demonstrate that the SARS-CoV-2 infection attenuates the immunosurveillance against tumors that may increase the tumor incidence or tumor recurrence in COVID-19 patients.

2) SARS-CoV-2 infection promotes pro-tumoral inflammatory responses

Tumor-promoting inflammation is one of the main characteristics of cancers. Both chronic and acute inflammation potently affect cancer development [59]. The inflammatory-related mediators can aid tumor development through inducing cell proliferation, angiogenesis, DNA damage, cytoskeleton remodeling, and degradation of the extra-cellular matrix [59-61]. Inflammation may promote metastasis by producing mediators that enhance vascular permeability [62]. Some cytokines present in the tumor microenvironment, such as IL-6 and TNF-α, and epiregulin can enhance the survival of the metastatic cancer cells [63].

Hyperinflammatory responses and elevated quantities of inflammatory cytokines are hallmarks of the severe form of COVID-19 [4,28]. Cytokine storm is a harmful systemic inflammatory reaction emerging from the releasing of the vast amounts of pro-inflammatory cytokines and chemokines, which operate a crucial role in the occurrence of some main SARS-CoV-2-related complications, such as ARDS [4]. TNF-α and IL-6 are the main players of cytokine storm that were correlated with COVID-19 severity [64-66]. The IL-6 and TNF-α concentrations are inversely associated with lymphocyte count, which means that the cytokine syndrome may dampen the specific immune response against SARS-CoV-2 infection [64,65]. TNF-α and IL-6 promote carcinogenesis and contribute to metastasis, tumor invasion, and angiogenesis [59,67]. Hospitalized subjects with cancer who have elevated IL-6 and TNF-α levels are at greater risk of death [68]. Both cytokines may play key roles in the tumor progression in malignant patients infected with SARS-CoV-2. Reducing the development of tumors in COVID-19 patients by targeting IL-6 and TNF-α needs to be clarified in future studies.

Elevated levels of the chemokines including CCL2, CCL4, CXCL8, CXCL9, and CXCL10 have been also demonstrated in patients with COVID-19 patients [28,69]. The mentioned chemokines could contribute in cancer development via several mechanisms such as tumor cell expansion, cancer stem cell proliferation, metastasis, angiogenesis, tumor invasion, epithelial-mesenchymal transition (EMT) induction, MDSC attraction, and fibroblast recruitment [70,71]. The appearance of various subsets of MDSCs was indicated in COVID-19 patients correlating with viral load and disease severity [72-74]. Hence, the elevated expression of the chemokines can support tumor progression in malignant patients with COVID-19. Thus, targeting tumor-promoting chemokines or blocking their receptors could reduce tumor progression.

ACE2 exerts anti-inflammatory and anti-oxidative effects during infection [4]. The SARS-CoV-2-dependent depletion of ACE2 potentiates the pro-inflammatory and oxidative impacts of angiotensin II[4]. Oxidative stress acts as a starter and enhancer of carcinogenesis as this phenomenon promotes cell proliferation, tumor invasion, angiogenesis, tumor cell survival, chemo-resistance, and radio-resistance[75].

3) SARS-CoV-2 can exert direct oncogenic impacts

A direct relation has been postulated between coronavirus infection and dysregulation of the cell cycle leading to the cellular transformation. The Nsp3 and Nsp15 of SARS-CoV have been implicated in the degradation of the tumor suppressor proteins P53 and retinoblastoma (pRb), respectively[76,77]. Similarly, Nsp3 and Nsp15 of SARS-CoV-2 can affect tumor suppressor proteins. The results from an in silico analysis indicated that the S2 subunit of SARS-CoV-2 potently interacts with tumor suppressors P53 and BRCA1/2 [78].

SARS-CoV-2-induced alteration in the activity of E2F transcription factors and RB1 can also promote malignancies. Rb controls the movement from the G1 phase to the S phase in the cell cycle by modulating the E2F activity[79]. The RB1 activity was remarkably reduced, whereas the activity of E2F was enhanced in COVID-19 patients indicating that SARS-CoV-2 may inactivate tumor suppressor Rb resulting in the elevated E2F activity that promotes cell proliferation same as some other oncogenic viruses[79].

The MAPK, JAK-STAT and NF-κB-mediated signaling pathways may also contribute to the tumorigenesis in SARS-CoV-2-infected individuals. The SARS-CoV-2-derived molecules, such as S protein can be identified by some TLRs such as TLR2, which activates the transcription factors NF-κB and MAPKs through recruitment of MyD88 [80,81]. Furthermore, JAK-STAT signaling pathway is activated following the binding some cytokines to their relevant receptors [45,65]. The involvements of the MAPK and JAK-STAT-mediated signaling pathways in the development of numerous cancers have been indicated [82]. The targeting of MAPK and JAK-STAT-mediated signaling pathways may interfere with tumorigenesis [82,83].

4) Possible reactivation of oncogenic viruses may lead to cancer development after SARS-CoV-2 infection

Infections play a key role in the development of human malignancies, as about 15.0% of cancers are attributed to oncogenic infectious agents [84]. Some infectious agents such as HTLV-1, HPV, EBV, and KSHV cause latent infection, where most infected persons are asymptomatic [85]. The viral oncoproteins exclusively produced in HTLV-1-, HPV-, EBV-, and KSHV-infected cells support cell proliferation [84,85]. However, HIV itself may have not a direct oncogenic impact, but it increases the risk of cancers by enabling oncogenic agents to expand in co-infected individuals [85]. Similarly, SARS-CoV-2-mediated immune impairment may allow oncogenic pathogens to transform normal cells into malignant cells. It has been reported that some SARS-CoV-2-related proteins and some therapeutic agents can reactivate KSHV which may enhance the risk of cancer development, even in fully recovered COVID-19 patients [86]. Furthermore, the possible presence of SARS-CoV-2-derived oncoproteins that can transform the normal cells into malignant cells needs to be clarified in future studies.

Malignancy promotes the COVID-19 severity

As mentioned above, in innate immunity, IFNs including type I and type III IFNs, serve as the first line of protection against viruses such as coronaviruses [45,87]. An early proper IFN response can effectively control SARS-CoV-2 infection[28,45]. Following the initial innate response, induction of an appropriate adaptive immune response is also necessary to clear SARS-CoV-2 and prevent disease progression to severe phases [28,88]. Both innate and adaptive immune responses are impaired in malignant patients [89]. Lymphopenia (an independent poor predictor in COVID-19 patients) is common in cancer patients who are under active or even watchful treatment [90]. Thus, the immunocompromised state in cancer patients makes these patients more susceptible to COVID-19, and SARS-CoV-2-infected cancerous patients exhibit more severe complications of COVID-19 [91].

The infection rate of SARS-COV-2 in cancer patients is greater than the general population, and cancer patients with COVID-19 showed worsening symptoms and bad outcomes [92]. Malignant patients with COVID-19 display a greater risk of developing serious and even deadly respiratory disorders [93]. It has also been observed that patients with hematological cancers exhibit more serious COVID-19-related complications and more deaths compared with non-malignant care professionals with COVID-19 [94]. The patients with lung cancer also

develop severe COVID-19-related lung complications and therefore are at higher risk of dying from SARS-CoV-2 infection [95]. The ACE2 upregulation was commonly found in patients suffering from lung cancer. As a result, the increased ACE2 expression in lung cancer could likely promote the susceptibility of lung cancer patients to SARS-CoV-2 infection [96].

CONCLUSION

SARS-CoV-2-mediated immunosuppression, hyper-inflammation, and oxidative stress may direct and/or indirectly promote the development of some cancers in predisposed individuals who are infected with SARS-CoV-2 (Figure 1). Furthermore, downregulation of the tumor suppressor proteins and possible reactivation of latent oncogenic viruses in COVID-19 patients can enhance the risk of certain cancers after SARS-CoV-2 infection. The possible presence of the oncogenes in the SARS-CoV-2 needs to be evaluated in future studies. Some COVID-19 patients experience prolonged manifestations which may persist for several months after infection [6,7]. Moreover, clinically recovered COVID-19 individuals display profound immunologic alterations that extend several months after discharge [21-23]. Thus, SARS-CoV-2-infected individuals, especially chronic cases, may need post-infection monitoring for cancer development. On the other hand, patients with malignancy are more vulnerable to SARS-CoV-2 and are at higher risk of developing severe symptoms of COVID-19 (Figure 1). Therefore, SARS-CoV-2-infected cancerous patients may be at greater risk of death from COVID-19-related complications. It should also be noted that COVID-19 and malignancy may have some similarities regarding their pathogenicity. Therefore, the identification and the targeting of common pathways between COVID-19 and cancers need more attention in an attempt to treat both diseases using similar therapeutic agents. Ultimately, even during a pandemic, cancer patients need a timely diagnosis, treatment, and monitoring. Moreover, the major risk for cancerous patients in the COVID-19 outbreak may be due to the inability to earn sufficient healthcare facilities [97].

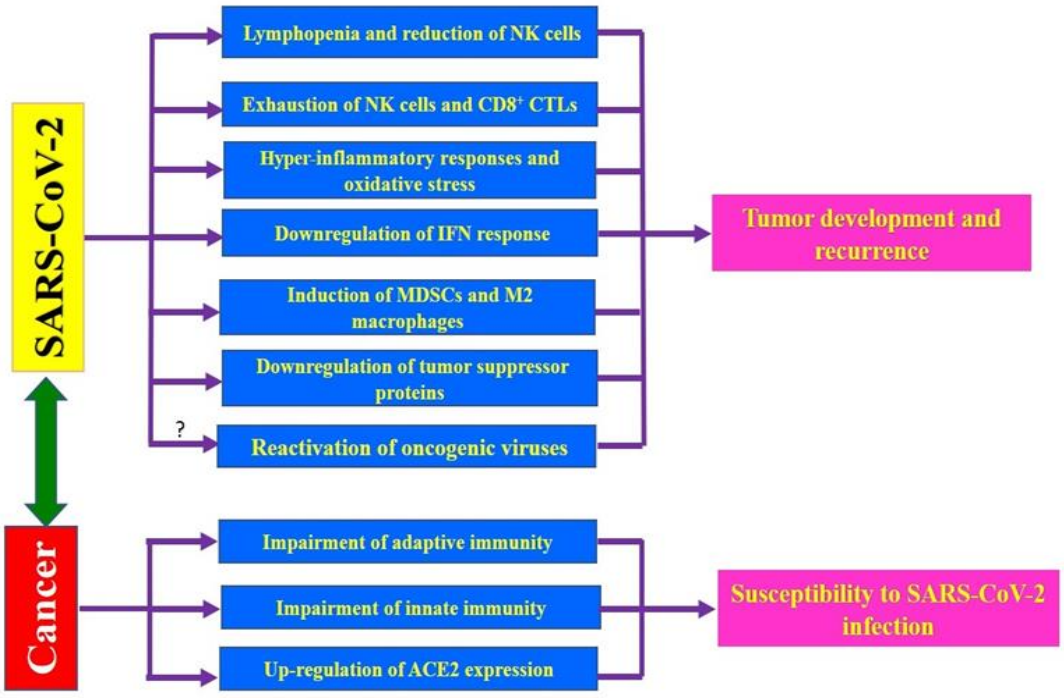

Figure 1: Impacts of COVID-19 and cancer on each other. The SARS-CoV-2 infection may enhance the risk of cancer development and recurrence through induction of exhaustion of cytotoxic lymphocytes, stimulation of hyper-inflammatory responses, induction of oxidative stress, reduction of the number of lymphocytes and NK cells, down-regulation of IFN response, induction of the pro-tumoral cells such as MDSCs and M2 macrophages, downregulation of tumor suppressor proteins, and perhaps through re-activation of the oncogenic viruses. On the other side, the malignancy can enhance the susceptibility to SARS-CoV-2 infection and increases the severity of COVID-19-related complications through impairing both innate- and adaptive immune responses to virus as well as upregulation of angiotensin-converting enzyme 2 (ACE2) in certain cancers such as lung cancer.

CONFLICTS OF INTEREST

The authors declare no conflict of interests.

Abbreviations

ARDS: Acute respiratory distress syndrome
COVID-19: Novel coronavirus disease 2019
EBV: Epstein-Barr virus
HIV: Human immunodeficiency virus
HPV: Human papillomavirus
HTLV-1: Human T-cell lymphotropic virus type 1
ICU: Intensive care unit
IFN: Interferon
JAK–STAT: Janus kinase-signal transducer and activator of transcription
KSHV: Kaposi sarcoma-associated herpesvirus
MAPK: Mitogen-activated protein kinase
MHC: Major histocompatibility complex
MyD88: Myeloid differentiation factor 88
NF-κB: Nuclear factor kappa B
SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2
TNF: Tumor necrosis factor

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