Chapter

COVID-19 and Cancer: Biological Interconnection and Treatment

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Abstract

The COVID-19 pandemic has affected more than 125 million lives worldwide and more than 2.5 million people have died so far. Cancer in itself increases the risk of infection especially, cancer patients undergoing cancer-associated treatments are more susceptible to SARS-CoV2 infection. However, many questions related to the biological interconnection between the two diseases remain to be answered. This chapter summarizes some of the biological components that connect cancer to COVID-19 and provide knowledge to not only understand but also, target the co-morbidities.

Keywords: COVID-19, cancer, viral infections, chemotherapy, radiotherapy, immunotherapy, cytokine storm, coagulopathy, ACE2, TMPRSS2

1. Introduction

For past many decades, viral infections have presented a great challenge for cancer patients, on the delivery of cancer care, cancer research, and oncologists. COVID-19 caused by SARS-CoV2 virus continues to spread around the globe and more than 1 million people have been killed due to COVID-19 worldwide (at the time of writing). Though majority of infected people will recover, cancer patients remain at a higher risk to SARS-CoV2 infection and its related severe outcomes. Cancer patients are reported ~3 times more susceptible to SARS-CoV2 infection with possible poor outcomes than individuals without cancer potentially due to their systemic immunosuppressive state caused either by malignancy itself or the anti-cancer treatments. Moreover, the mortality rate of SARS-CoV2 positive cancer patients was reported 6% than 1% for non-cancer patients in China. However, a limited research has been done to understand the biological interconnection between cancer and viral infections. Especially, little is known about the SARS-CoV2 infection biology Therefore, studying whether and how SARS-CoV2 affects cancer and its progression and, vice versa is of utmost importance for (1) the better management of SARS-CoV2 infected cancer patients and, (2) developing novel treatment strategies that can target SARS-CoV2 and/or cancer.

2. Linking viruses and cancer

Viruses are the smallest microorganisms made up of a small number of genes in the form of DNA or RNA surrounded by a protein coating. Viruses enter into a living cell and hijack it's cellular machinery in order to make more copies of itself.

When a virus enters the body, it triggers the body's immune system. These immune defenses begin with white blood cells which learn to attack and destroy the virus or the virus infected cells. If the body survives the virus attack, the immune system's memory is able to respond more quickly and effectively to subsequent infection by the same virus. This response is called Immunity. Immunity can also be triggered by getting a vaccine. Viruses can be divided into three classes: oncogenic, oncolytic and, non-oncogenic non-oncolytic viruses. The oncogenic viruses (for example, hepatitis C virus, human T-lymphotropic virus, hepatitis B virus) change cells by either integrating their genetic material with the host cell's DNA or enhancing already existing oncogenic genes within the host genome. Thus, the infected cell is regulated by the viral genes and has the ability to undergo abnormal growth. Conflicting results for the relationship between different viruses and various cancer sub-types have been stated in pre-clinical and clinical settings. This is due to the reason that the course and outcome for both, viral infections and cancer and regulated by the type of viral infection, type of cancer and the immune system components involved. For example, a faster growth of melanoma was observed in mice that were challenged with H1N1/influenza A virus due to shunting or diversion of cytotoxic T cells from tumor site to the viral infection site. On the contrary, a slower growth of Lewis lung carcinoma cells was observed in mice following influenza virus infection. Thus, more studies need to be undertaken for clearer context dependent results. Both viruses and cancer invade our normal healthy systems for their growth and proliferation. The inability of our immune system to distinguish between self and non-self, links the severe pathogenesis associated with cancer and viral infections.

3. COVID-19

Coronaviruses are a large family of viruses that can cause mild illnesses, such as the common cold, to more severe diseases such as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). Coronaviruses take their names from the distinctive spikes with rounded tips around their surface, which reminded virologists of the appearance of the sun's atmosphere, known as corona. Coronaviruses are known to primarily target the human respiratory system. COVID-19 represents the seventh member of the coronavirus family that infects humans. Because the novel coronavirus is related to the SARS-associated coronavirus (SARS-CoV), the virus has been named SARS-CoV2. SARS-CoV2 infection may result in mild to severe symptoms that may develop between 2 and 14 days after exposure to the SARS-CoV2 virus. The symptoms of COVID-19 may include shortness of breath, chills, fever, cough, headaches, sore throat, and loss of taste or smell. Additional symptoms including aches, fatigue, nasal congestion and diarrhea may also appear. The illness may cause severe pneumonia and heart problems in some people and may also lead to death. Some people may not develop any symptoms following infection.

SARS-CoV2, by using the spike-like protein on its surface, binds to ACE2 (Angiotensin converting enzyme 2) prior to entry and infection into the host cell. Thus, ACE2 acts as a doorway for the virus that causes COVID-19. ACE2 is a carboxypeptidase enzyme present on the surface of many cell types in tissues like, lungs, heart, blood vessels, kidneys, liver and gastrointestinal tract. The function of ACE2 is to generate small peptides/proteins by cutting up the larger protein angiotensin which then go on to regulate functions in the cells involving wound healing, inflammation and blood pressure regulation, etc.

4. Cancer

Cancer is a broad term for a class of diseases characterized by uncontrolled growth and proliferation of abnormal cells. These normal cells have the ability to infiltrate and destroy normal tissues. The types of treatments that one receives depend on the type of cancer and how advanced it is. Mostly it is a combination of treatments such as chemotherapy, radiotherapy, immunotherapy, hormonal therapy, stem cell transplantation and other targeted therapies. Cancer on its own and its treatment using chemotherapy or radiotherapy weakens one's immune system, reducing the number of infections fighting immune cells and making it harder for one's body to fight infections including the viral infections. And this is why cancer patients who are undergoing or recently underwent chemo/radiotherapy are particularly at higher risk.

5. COVID-19 and cancer

COVID-19 by itself remains biologically novel and not much is known about the role of novel coronavirus SARS-CoV2 in cancer. Some critical questions that need to be answered are (1) Whether SARS-CoV-2 infection cause cancer? (2) Whether SARS-CoV-2 infection increases the risk of cancer? and, (3) Whether SARS-CoV-2 infection affects the survival of cancer patients?

Similar to other severe acute respiratory outbreaks (SARS-CoV, MERS-CoV), comorbidities such as hypertension and malignancy predispose COVID-19 positive patients to adverse clinical outcomes [1–4]. Whether SARS-CoV2 causes or modulates cancer pathobiology, is unknown. However, it is evident that patients undergoing cancer-associated treatments for example, chemo or radiotherapy and CAR-T cell therapy patients are at higher risk of becoming worse following COVID-19 infection [5, 6]. A recent study including 1,590 COVID-19 positive patients in China shows cancer as one of the more serious comorbidities that increase risk with respect to COVID-19 [4, 7]. Therefore, cancer patients receiving anti-tumor therapies should have vigorous screening for COVID-19 infection and their immunosuppressive treatment regimens and dosages potentially decreased in the case of COVID-19 co-infection [8]. For some patients, chemotherapy must be postponed until completion of the antiviral course of therapy, while others cannot be subjected to the viral infection therapy while under treatment for their cancer [9]. The symptoms of COVID-19 in cancer patients are mostly similar to the ones in general population (fever, coughing and shortness of breath) [10, 11]. However, cancer-associated treatments for example, steroids may suppress the fever symptom of COVID-19. The decision on treatment of a COVID-19 positive cancer patient depends on the type of cancer, stage of treatment, and severity of COVID-19. Immune dysregulation and chronic inflammation may be potential drivers of severe outcomes in COVID-19-positive cancer patients. Therefore, a better understanding of the mechanistic link between the two will help to prevent negative effects of infection and also enable the design of novel therapies that target cancer and COVID-19, and co-target both diseases.

6. The biology of interconnection between COVID-19 and cancer

The biological connection between COVID-19 and cancer remains an understudied area. However, age, ACE2, cytokine storm, and coagulopathy are few strong connecters that link COVID-19 with cancer. A better understanding of these linkers may help us find novel therapy options for the comorbidities.

6.1 Age

Our risk of getting cancer increases with age mostly due to accumulation of mutations with our prolonged exposure to mutagens. In addition, as we grow older, our body's immune system and DNA damage repair system get weaker [12]. In a similar fashion, age has turned out to be a poor prognostic factor for COVID-19 patients. This suggests that age plays a similar role in the progression and pathogenesis of cancer and COVID-19. Further studies should be conducted to identify the molecular interconnection between age, cancer and COVID-19.

6.2 Angiotensin converting enzyme 2 (ACE2)

ACE2 is a carboxypeptidase enzyme that converts angiotensin I to angiotensin 1–9 and angiotensin II to angiotensin 1–7. It is involved in the regulation of heart function and in the protection during acute lung injury [13–15]. SARS-CoV-2 enters human cells through angiotensin 1 converting enzyme 2 (ACE2) [16, 17]. The virus enters via this spike protein, binds to ACE2, and together with ACE2 enters the cell, fuses to the membrane, the virus exists the endosome, and replicates [18]. ACE2 is expressed in multiple organs, including cardiovascular, respiratory, urinary and digestive systems in healthy individuals. The expression levels of ACE2 in cellular subtypes is shown to be viral infection- and interferon-driven [19–21]. Notably, the expression levels of ACE2 are different in cancer cells. According to a recent clinical study, the expression levels of ACE2 gradually increase from healthy control, adenoma, to colorectal cancer patients. This indicates that cancer patients are more likely to be infected with SARS-CoV2. Patients with tumors, expressing higher levels of ACE2, are more susceptible to SARS-CoV2 infection and have poor prognosis [19, 22, 23]. Renal tissue shows higher expression levels of ACE2, and this might explain why most COVID-19 patients have renal dysfunction [18, 24]. Decreased levels of ACE2 were reported in non-small cell lung cancer (NSCLC), and its overexpression had a protective effect in NSCLC and breast cancer via inhibiting cell growth and angiogenesis [25–27]. Due to limited research done in this area, it would be worthwhile to test whether levels of ACE2 increases or decreases in various tissues of cancer patients and COVID-19 patients and how this impacts COVID-19 infection in these patients.

6.3 Cytokine release syndrome

Cytokine release syndrome (CRS) or cytokine storm is a systemic inflammatory response. Cytokine storm can be triggered by pathogenic infections, certain drugs, antibody treatments and, chimeric antigen receptor (CAR)-T cell therapy [28, 29]. Cytokine storm induction is the main cause of inflammation in SARS-CoV-2 infection. Upregulation of cytokines for example, interleukin-6 (IL-6), interleukin-1 beta (IL-1β) in serum, tumor necrosis factor-alpha (TNF-α) are found in COVID-19 patients. Elevated levels of lactate dehydrogenase, and increased levels of circulating monocytes are also common in COVID-19 patients [30, 31]. Such elevated levels of pro-inflammatory cytokines are also observed in cancer patients undergoing immunotherapy and CAR-T cell therapy [32]. The cytokine levels in cancer patients undergoing immunotherapy are higher than the cytokine levels in COVID-19 patients experiencing acute respiratory disease syndrome. The understanding of oncologists in regulating severe inflammatory reaction may prove highly beneficial in these settings. Therefore, anti-inflammatory therapies currently used for cancer patients may be repurposed for the treatment of COVID-19 patients.

6.4 Coagulopathy

Bleeding complications including thrombosis are leading causes of death in cancer patients. Thrombotic events are also commonly associated with the morbidities in COVID-19 patients. Cancer/tumor cells release cytokines, cysteine proteases, tumor micro particles and other pro-coagulants in their microenvironment. Release of such biomolecules can cause an imbalance in hemostasis [33]. Increased levels of D-dimer and prothrombin and decrease in fibrinogen is reported in COVID-19 non-survivor patients at days 10–14 [34–36]. This highlights the significance of regular monitoring and maintenance of these factors in COVID-19 and cancer patients. Therefore, further insights into the molecular interconnections of COVID-19 and cancer disease conditions to coagulopathy may help in reducing the associated mortality in these patients.

6.5 TMPRSS2

Transmembrane Serine Protease 2, TMPRSS2 presents another potential point of connection between cancer and COVID-19. In prostate cancer TMPRSS2 is regulated by the androgen receptor, and the androgen receptor is found not only on prostate cells but on cells of the lung as well. Further investigation is needed to confirm whether the receptor regulates TMPRSS2 in lung tissue, but if it does, androgen-targeted therapies, which are used in the treatment of prostate cancer, could limit SARS-CoV2 infection by downregulating TMPRSS2.

7. Therapeutic options in COVID-19 and cancer patients

Previous studies suggest conflicting results on whether anti-cancer and anti-COVID-19 therapies can be co-administered safely. For example, in over 1000 HCV-positive breast cancer patients, chemotherapy was shown feasible with no significant side effects [37]. However, in another study, ovarian cancer patients undergoing chemotherapy were unable to generate antibody response to the influenza vaccination [38]. Therefore, further efforts are needed to investigate the efficacy and safety of co-administration of anti-cancer and anti-viral drugs and how these outcomes are dependent on the type of cancer, viral infection and therapy.

Vaccination is the most promising approach for preventing a viral infection. Pharmaceutical industries and research organizations across the globe have put great efforts in developing effective and novel vaccine candidates to neutralize SARS-CoV2 virus. Additionally, strategies like repurposing direct preexisting anti-viral drugs as well as convalescent serum from COVID-19 recovered patients have been effectively used. Different monoclonal antibodies (mAbs) that recognize the different epitopes on the viral surface may have improved efficacy in neutralizing the SARS-CoV2 virus. IL-6 inhibitors (for example, tocilizumab and siltuximab mAbs) have been used for the management of cytokine storm in cancer patients receiving CAR-T cell therapy. IL-1, a cytokine upstream of IL-6 which is also upregulated in CRS and IL-1 receptor antagonists such as anakinra have been used to treat arthritis patients. Another class of drugs are nontoxic immune-suppressants known as calcineurin inhibitors that impair T-cell function and thereby reduce cytokine levels. Various viral gene components fundamental for the unchecked proliferation of virus in host cancer cells can serve as therapeutic targets for effective anti-viral therapies. Studying these critical viral components will help the researchers to understand the interconnection between the biology of COVID-19-infected cancer versus normal host cells.

The role of various immune cells for example, T cells, and natural killer (NK) cells in understanding the pathology and therapies of cancer and viral infections is becoming more evident with time. This motivates scientists to enhance their understanding and develop novel immunomodulatory therapeutic strategies for co-targeting these diseases. Functional natural killer (NK) cells can produce antiviral responses against influenza infection and are also reported as potential anti-cancer agents. Additionally, due to their negligible graft vs. host signature, NK cells may provide a safer alternative to co-target cancer and COVID-19. Nanoparticles present excellent vehicles for delivering various disease-associated payloads in vivo. Nanoparticles ornated with recombinant human ACE2 protein on their surface may provide an effective therapeutic option for COVID-19 patients. Following binding to the spike protein of SARS-CoV2 virus, ACE2-conjugated nanoparticles may neutralize the virus and prevent it from binding to the ACE2 receptor present on host cells. Conventional anti-cancer treatment strategies, such as chemo or radiotherapy are unable to distinguish between cancer cells and normal cells. This is a significant drawback and leads to toxicities for patients undergoing treatment. Therapies that directly target viral proteins or generate immune responses against infected cells or cancer cells hold promise for effective and tolerable treatment strategies.

8. Future research perspectives

To understand the pathogenesis of COVID-19 and to connect the link between cancer and COVID-19, we need to develop and study suitable animal models that represent the comorbidity of different cancers and COVID-19 in patients with accuracy. Additionally, the role of specific SARS-CoV2 proteins may be studied by developing chimeric mouse models that express SARS-CoV2 proteins in some tissues. Ziegler et al. demonstrated that ACE2 expressing human cells are the primary targets for SARS-CoV2 infection and that human ACE2 expression in epithelial cells is interferon dependent [20]. Especially, a significantly weaker induction of murine ACE2 was observed in response to interferon or viral infection [20]. Thus, humanized models permissive to SARS-CoV2 infection would closely mimic the human disease condition. Investigating and identifying the relevant immune constituents may lead to new biological strategies to target co-morbidities associated with viral infections and cancer patients. Determining whether active SARS-CoV2 virus leads to cancer in mice would also be an interesting scientific to avenue to better understand the pathology of SARS-CoV2. Clearly, the learnings from cancer biology and cancer therapeutics research will help in establishing clinically effective treatment options for COVID-19 patients (**Figure 1**). It would also be of high relevance to include and study the role of demographic factors in context of cancer and COVID-19 comorbidities.

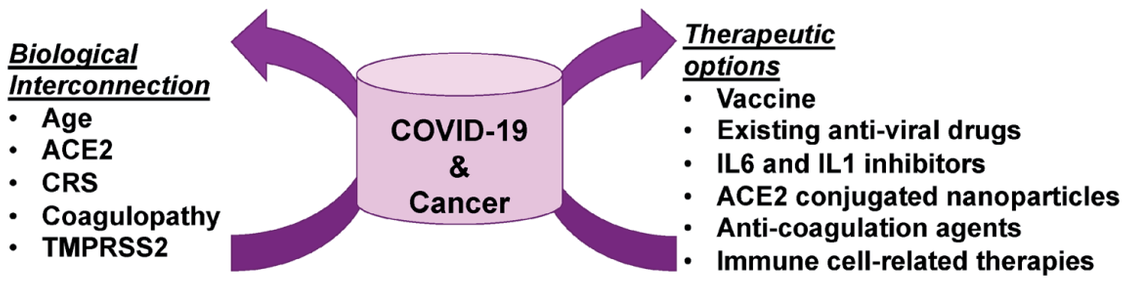

Figure 1.
Interconnection between COVID-19 and cancer.

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