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SARS-CoV-2 and cancer: the intriguing and informative cross-talk

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ABSTRACT

The COVID-19 pandemic caused by the SARS-CoV-2 virus has significantly disrupted and burdened the diagnostic workup and delivery of care, including transfusion, to cancer patients across the globe. Furthermore, cancer patients suffering from solid tumors or hematologic malignancies were more prone to the infection and had higher morbidity and mortality than the rest of the population. Major signaling pathways have been identified at the intersection of SARS-CoV-2 and cancer cells, often leading to tumor progression or alteration of the tumor response to therapy. The reactivation of oncogenic viruses has also been alluded to in the context and following COVID-19. Paradoxically, certain tumors responded better following the profound infection-induced immune modulation. Unveiling the mechanisms of the virus-tumor cell interactions will lead to a better understanding of the pathophysiology of both cancer progression and virus propagation. It would be challenging to monitor, through the different cancer registries, retrospectively, the response of patients who have been previously exposed to the virus in contrast to those who have not contracted the infection.

1. Introduction

SARS-CoV-2, a novel ssRNA human-infecting coronavirus, broke out in Wuhan (China) in late 2019 and subsequently spread, leading to the current worldwide pandemic of its associated disease COVID-19. Its spread to vulnerable cancer patients has influenced their care and conferred a worse prognosis with higher morbidity and mortality. The mechanisms through which viruses in general and SARS-CoV-2 specifically interact with cancer cells are of great interest, and their understanding will influence both cancer care and antiviral therapy.

2. Viruses and cancer

In 1910, Peyton Rous demonstrated that chickens developed cancer when injected with material extracted from a cancer tumor of a diseased hen and concluded that cells from the hen's tumor contained an infectious substance, a virus, that transmits cancer. It was not until the mechanism of action of viruses on the genome was understood that Rous' discovery was reignited, warranting him a Nobel Prize in 1966. Over the last 50 years, significant milestones have been achieved in tumor virology [1]. The mechanisms through which viruses interact with tumors are numerous. Viruses can be oncogenic, directly implicated in the neoplastic process or suppressing the immune system, paving the way for the development of malignancy or persistently challenging the immune system resulting in an immune clonal expansion and lymphomagenesis. They can, on the other hand, infect and kill cancer cells or be opportunistic, flaring when the body's immune system is suppressed by the spreading tumors or under the effect of anticancer therapy [2,3].

Currently, at least seven human cancer oncogenic viruses have been identified, with recent advances in molecular technologies enabling the discovery of new potential ones [1]. It is well known now that infectious agents cause one fifth of human cancers and that 12 % of cancers are causally linked to oncogenic viruses [4]. The ubiquitous Epstein-Barr virus (EBV) is a herpesvirus linked to Burkitt's lymphoma or nasopharyngeal carcinoma [5]. The relation between the blood-borne hepatitis B virus and acute and chronic liver infections, liver failure, cirrhosis, and hepatocellular carcinoma (HCC) has also long been described [6]. As for hepatitis C, a flavivirus, eighty-five percent of infected adults develop chronic infection, which leads to cirrhosis and HCC [7]. Furthermore,

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hepatitis C has been implicated in the process of lymphomagenesis [8,9]. Human papillomaviruses are also established etiological agents of human cancer [10] and the retroviruses, human T-cell leukemia virus type 1 and HIV have also been labelled as oncogenic viruses [11,12]. Emerging technologies allowed the identification and characterization of the DNA sequence of the Kaposi's sarcoma-associated herpesvirus (KSHV), a member of the gamma herpes viruses [13] and the most recent human oncogenic virus to be discovered is Merkel cell polyomavirus (MCV) causing the rare, but highly aggressive neuroectodermal tumor, Merkel cell carcinoma (MCC) [14]. So, the link between virus infection and cancer is established.

On the other hand, some viruses tend to infect and kill tumor cells. Known as oncolytic viruses (OVs), this group includes viruses found in nature and agents modified in the laboratory to reproduce efficiently in cancer cells without harming healthy cells. Herpes simplex virus, adenovirus, and Coxsackievirus have different clinical applications in cancer treatment [2]. OVs can achieve their targeted treatment effects through selective cell death and induction of specific antitumor immunity [15].

Another group of viruses interacts with immunosuppressed cancer patients, potentially inducing secondary oncogenicity. *De novo* opportunistic viral infections or reactivation of dormant ones like cytomegalovirus, EBV, Varicella-Zoster, Hepatitis B and C as well as BK polyomavirus have all been reported in immunocompromised cancer patients worsening their prognosis but are unlikely to interact directly with cancer cells [3,16]. Many of these opportunistic viruses are oncogenic and can induce a secondary malignancy. Therefore, one can postulate that widely spreading viral infections can have a substantial direct or indirect role in developing a new course of an existing malignancy.

3. SARS-CoV-2

SARS-CoV-2, a novel ssRNA human-infecting coronavirus, broke out in Wuhan (China) in late 2019 and subsequently spread, leading to the current worldwide pandemic of its associated disease COVID-19. SARS-COV-2 belongs to the β-coronaviruses genus, has an envelope, is 60–140 nm in diameter and is round or oval. It enters the human body via the airway tract, infecting both the epithelial cells of the airway tract, as well as the resident, infiltrating and circulating cells of the immune system [17]. SARS-CoV-2 enters host cells via the angiotensin-converting enzyme 2 (ACE2). It is an RNA virus sharing some characteristics with other well-known RNA viruses' such as HIV, HCV and influenza viruses [18]. To date, it has infected more than 500 million individuals across the globe [19].

4. SARS-CoV-2 and cancer interactions

4.1. SARS-CoV-2 and cancer, a bidirectional relation

The COVID-19 pandemic has significantly disrupted the diagnostic workup and delivery of care to cancer patients and its burden was immense [20,21]. Furthermore, early analysis pointed out that those patients with cancer contracting COVID-19 had a higher probability of death compared with patients without cancer [22]. In studies that included solid cancer patients, those who got COVID-19 also had a higher probability of death compared with patients without cancer [23]. Immunosuppressed patients with hematologic malignancies had a 2.5-fold increased risk of mortality from COVID-19 infection [24]. Furthermore, SARS-CoV-2 clearance times differ substantially depending on the criteria used and may be prolonged in cancer patients [25].

COVID-19 infection and malignancy share the features of thromboinflammation with the generation of platelet (pEVs) and other cell-derived extracellular vesicles (EVs) [26]. In COVID-19 infection, COVID-19 leads to T-cell depletion and lymphopenia. Intimate crosstalk exists between malignancy and the platelets with the generation of pEVs [27,28]. Malignancy, therefore, contributes to the generation of EVs and pEVs; it is thus postulated that a concomitant SARS-CoV-2 infection in a malignant patient would amplify the pEVs and EVs generation. Zahran et al., studied total EVs, pEVs, endothelial EVs (eEVs), CD62 activated platelets, and CD41 platelet markers in 23 patients with active cancer infected with SARS-COV-2, as evident by a positive PCR, compared to patients with COVID-19 infection in the absence of malignancy and normal healthy control volunteers' [29]. Although COVID-19 malignant patients had significantly lower platelet counts than COVID-19 non-malignant ones, their total EVs and eEVs were considerably higher, with no significant difference in pEVs between both groups. Yet, both groups had a considerable accumulation of total EVs, pEVs, eEVs, and activated platelets compared to healthy controls [26]. The enhanced thromboinflammation in COVID-19 cancer patients has likely contributed to the increased mortality among this patient group [22].

The genomic alterations of six SARS-CoV-2 receptor-related regulators [transmembrane serine protease 2 (TMPRSS2), angiotensinogen (AGT), ACE1, solute carrier family 6 member 19 (SLC6A19), ACE2, and angiotensin II receptor type 2 (AGTR2)] and their clinical relevance across a broad spectrum of solid tumors were also evaluated across 33 cancers. This may clarify the potential mechanisms of tumorigenesis and provide a novel approach to cancer treatments [30]. Furthermore, four major similar signaling pathway, have been identified at the intersection of COVID-19 and cancer; namely, cytokine, type I interferon (IFN-I), androgen receptor (AR), and immune checkpoint signaling. In COVID-19 infection, more than 50 cytokines have been described in the context of the pro-inflammatory cytokine storm, particularly interleukin 6 which is reported to be aberrantly hyperactivated in many types of cancers [31].

The cell-to-cell transmission of SARS-CoV-2 is also an interesting phenomenon that may contribute to its interaction with cancer cells. The spike protein of SARS-CoV-2 mediates the viral cell-to-cell transmission, with cell-cell fusion contributing to cell-to-cell transmission, yet ACE2 is not required [32]. The roles played by the EVs in the cell-to-cell transmission of the virus and its infectivity to cancer cells are likely non-negligible [26].

4.2. SARS-CoV-2 and oncogenic potential

The question of the potential oncogenic role of SARS-COV-2 remains unclear and will only be answered over time. Policard et al. [33] identified genes modulated by COVID-19 infection implicated in oncogenesis, including E2F transcription factors and RB1; this finding suggests a mechanism by which SARS-CoV-2 infection may contribute to oncogenesis [33]. Such observations has not yet been validated in the clinical setting.

Many cancer patients who contracted COVID-19 were potential targets for opportunistic infections. Viral and fungal coinfections were infrequent among cancer patients with COVID-19, but were associated with very high mortality rates [34].

Remdesivir and molnupiravir are approved for treating COVID-19. However, little is known about their impact on the reactivation of concomitant dormant viral infections in COVID-19 patients. It seems that remdesivir, but not molnupiravir, induced lytic reactivation of Kaposi's sarcoma-associated herpesvirus (KSHV) and EBV, two major oncogenic herpesviruses, in one patient [35]. Data indicate that those KSHV+ patients, especially in endemic areas exposed to COVID-19 or undergoing treatment, may have increased risks of developing virus-associated cancers, even after they have fully recovered from COVID-19 [36].

Glioblastoma multiforme (GBM) has an increased incidence in elderly COVID-19 vulnerable individuals. SARS-CoV-2 might invade the brain directly via coronavirus receptors with little information about the role of the infection in the clinical development of GBM. The oncogenic roles of six coronavirus receptors (ACE2, DPP4, ANPEP, AXL, TMPRSS2, and ENPEP) in GBM were tested using bioinformatics and experimental

approaches. ANPEP and ENPEP were significantly increased at both the mRNA and protein levels in GBM compared with normal brain tissue. High expressions of *ANPEP* and *ENPEP* are associated with poor prognosis and survival. Moreover, all receptors are positively correlated with the immune infiltration levels of monocytes. Interestingly, Chen et al. [37] explored the association of coronavirus receptors with GBM and suggested ANPEP and ENPEP as potential therapeutic targets of GBM irrespective of COVID-19 [37].

The role played by the ACE2 in cancer progression or control remains controversial. A systemic investigation into associations between ACE2 and oncogenic pathways, tumor progression, and clinical outcomes in pan-cancer remains lacking. Computational analyses of associations between ACE2 expression and oncogenesis found that ACE2 upregulation was associated with increased antitumor immune signatures and PD-L1 expression, and favorable anti-PD-1/PD-L1/CTLA-4 immunotherapy response. ACE2 expression levels are inversely correlated with the cell cycle activity, mismatch repair, TGF-β, Wnt, VEGF, and Notch signaling pathways. Its upregulation, therefore, is associated with favorable survival in pan-cancer and in multiple individual cancer types [38]. On the other hand, ACE2 downregulation disrupts the renin-angiotensin-aldosterone axis (RAAS) and causes bradykinin accumulation that exerts a proliferative response via mitogen-activated protein kinase pathways with established roles in many types of cancers. SARS-Cov2, by affecting the RAAS and the immune system, has, therefore, the potential to induce tumor cell proliferation, apoptosis evasion, and dissemination, resulting in possible cancer progression [39]. ACE2 and the transmembrane serine protease 2 (TMPRSS2) are both involved in the SARS-CoV-2 infection process and are increased in the epithelium of the human prostate gland during the prostate carcinogenesis and are regulated by androgens. The risk of the SARS-CoV-2 infection and the severity of the disease in prostate carcinoma (PCa) patients treated with androgen deprivation therapy (ADT) was investigated. Four retrospective studies assessed the SARS-CoV-2 infection risk in PCa patients under ADT vs. no ADT. A non-significant association between the risk of SARS-CoV-2 infection and COVID-19 severity in PCa patients treated with ADT was reported [40].

4.3. SARS-CoV-2 and oncolytic potential

Paradoxically, SARS-CoV-2 could elicit an anti-tumor immune response and exert a potential oncolytic role in lymphoma patients [41]. As NK cells massively express ACE2, they are easily infected by SARS-CoV-2, resulting in a decline in cell numbers and loss of immune surveillance [42]. Many RNA viruses have demonstrated their capacity to induce NK apoptosis [43]. Therefore, the depletion and suppression of NK could serve as an adjuvant therapeutic tool for patients with resistant NK cell lymphoma [43]. Of interest is that the viral load of EBV-DNA, a sensitive biomarker of NK/T cell lymphoma, declines during COVID-19 and resurges as COVID-19 subsides [43]. Furthermore, recent studies have suggested that SARS-CoV-2 infection may protect against Hodgkin's lymphoma by eliciting an anti-tumor response [44].

5. Therapeutic implications

Four major signaling pathways are at the intersection of COVID-19 and cancer, namely, cytokine, type I interferon (IFN-I), androgen receptor (AR), and immune checkpoint interactions [31]. At the core of the cytokine pathway, Interleukin 6 (IL-6)-mediated JAK/STAT signaling consists of different distinct paths that induce the transcription of multiple target genes [45]. From the cancer perspective, several factors may contribute to IL-6-induced neoplastic changes [46], whereas from the COVID-19 perspective, the levels of Il-6 correlate with the viral load and lung injury, reflecting the severity and prognosis of this disease [47]. Selective inhibitors of nuclear export (SINE) medications such as selinexor and verdinexor, are potent blockers of XPO1 and have enriched the palette of therapeutic options for myeloma. Their safety and efficacy are currently tested in COVID-19 [48]. Interferons, on the other hand, are indispensable for immune responses against both cancer and viral infections [49]. The TMPRSS2 and androgen receptor pathways are also shared between prostate carcinoma and COVID-19. Interestingly, TMPRSS2 knockout mice are spared from severe infection and escape from lung diseases, highlighting the role of TMPRSS2 function in SARS-CoV-2 entry events [50] and the therapeutic potential of this axis. The role played by the PD-1/PD-L1 axis in both cancer and COVID-19 infection is also non-negligible. There is mounting evidence of upregulation of immune checkpoint receptors in severe COVID-19 cases associated with T cell exhaustion and lymphopenia [51]. Ex vivo blockade of PD-1 nearly normalized CD8 + T cells and restored T cell function, reverting the post-COVID-19 immune abnormalities [52,53]. Therefore, it seems evident that deeper knowledge of the different cancer proliferative pathways led to a better understanding of SARS-CoV-2 signaling with potential therapeutic applications for both COVID-19 and Cancer.

6. Conclusions

The COVID-19 pandemic has shaken the oncology world as patients who contracted the infection were at a greater risk of developing a severe and critical form of illness and suffered a poorer prognosis. Many centers opted to delay using high-dose chemotherapy or immunopotentiation therapies such as immune checkpoint inhibitors and CAR-T as they could aggravate inflammatory symptoms of patients with COVID-19. Furthermore, the overwhelmed health care system across the globe delayed diagnosis and postponed surgeries for many cancer patients, influencing their care.

We are now confronted with many cancer patients who have contracted SARS-CoV-2 and recovered from COVID-19. The long-term implications of SARS-CoV-2 infection on this population are still unknown. The effects of infection on pathways relevant to cancer could affect cell proliferation, development, and survival, favoring DNA degradation, preventing the repair of damaging events, and impeding the translation of RNA into functional proteins, and could lead to a more rapid disease progression [54]. In contrast, profound virus-induced immune modulation may have a beneficial effect on certain lymphomas.

The challenge of the coming years will be to track these patients through the different cancer registries and retrospectively monitor their disease path compared to those who did not contract the infection. It will also be of great interest to see if the pandemic has impacted the number of new cancer cases and the patterns of cancer development in the coming years. The data generated from these large databases will likely impact cancer care for decades to come.

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