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Potential of SARS-CoV-2 in Cancer Development: A Hypothetical and Mechanistic View

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ABSTRACT

The COVID-19 pandemic caused by the SARS-CoV-2 virus can lead to long-term health effects, such as possible oncogenic properties. The evidence shows that SARS-CoV-2 may affect cellular pathways involved in cancer development, such as chronic inflammation, immune evasion, and genomic instability. This review study explores the hypothetical mechanisms by which SARS-CoV-2 contributes to oncogenesis, including persistent viral infection, dysregulation of tumor suppressor genes (e.g. *p53*), activation of pro-oncogenic signaling (e.g. NF-κB, JAK/STAT), and induction of long-term oxidative stress. While the evidence of the link between SARS-CoV-2 and cancer remains limited, like other oncogenic viruses, including HPV and EBV, further investigation is needed. Further epidemiological and molecular studies are needed to validate these hypotheses and assess the potential oncogenic impact of SARS-CoV-2.

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Introduction

In late December 2019, cases of unexplained pneumonia in China, Wuhan were reported [1]. On January 21, 2020, the World Health Organization (WHO) provisionally designated the new coronavirus as coronavirus-2019 (COVID-19). Subsequently, the virus was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is an enveloped, non-segmented virus containing a single-stranded, positive-sense RNA genome, belonging to the Coronaviridae family [2]. Due to the pathogenesis of SARS-CoV-2 and the inflammatory response it triggers in the body, the virus may cause secondary complications that manifest in the long term. One of the potential long-term complications of SARS-CoV-2 could be carcinogenesis. Supporting this hypothesis, it has been estimated that about 15% of all human cancers worldwide are associated with viral infections. Both DNA and RNA viruses are capable of developing cancer in humans. In this regard, Epstein-Barr virus [3], human herpesvirus 8 [4], hepatitis B virus [5], and [6] are the four DNA viruses whose role in carcinogenesis has been indicated. Among the RNA viruses, Human T lymphotropic virus type 1 [7] and hepatitis C [8] viruses are known to contribute to human cancers. Given the importance of the issue and the worldwide distribution of SARS-CoV-2, the carcinogenic potential of this virus should be investigated. In this hypothetical article, we reviewed the possible mechanisms by which SARS-CoV-2 could be involved in cancer development.

SARS-CoV-2 and Potential Oncogenic Concerns

Along with previous studies, the role of SARS-CoV-2 in cancer development is suggested through theoretical extrapolations and confirmed via experimental evidence.

SARS-CoV-2 proteins and their oncogenic potential

The nonstructural protein 15 (NSP15) is a protein that is encoded by the SARS-CoV-2 genome. This protein plays a role in the coronavirus infection apart from its function as an endoribonuclease [9]. More importantly, the NSP15 can suppress apoptosis and thus affect the host cell processes. On the other hand, it is well-known that any disruption in programmed cell death (apoptosis) can result in uncontrolled cellular growth and subsequent cancer development. Therefore, it can be hypothesized that the *NSP15* gene can disrupt the mechanisms involved in the host cell death and pave the way for the survival of a carcinogenic cell. Furthermore, NSP15 can interact with the retinoblastoma (RB) protein, which is a tumor suppressor and plays an important role in preventing cancer. It has already been proved that some RNA viruses, such as HCV, can bind to the RB protein and induce its ubiquitin-mediated degradation, which can consequently lead to uncontrolled cell cycle progression and cancer development [10]. Moreover, NSP15 induces the expression of genes that are normally inhibited by RB and are involved in cell cycle promotion and cell proliferation [11]. In addition, the proteasomal digestion of RB is induced by the interaction between NSP15 and RB. Along with this overaction and rapid division, a dominant property is observed at higher levels of NSP15 expression [11].

Oxidative stress, DNA damage, epigenetic modifications, and signaling pathways

Studies have demonstrated that coronaviruses increase oxidative stress and inflammation. Previously, some studies reported stable epigenetic changes resulting from viral infections, such as HPV, HBV, and EBV [12]. The elevated oxidative stress and inflammation led to epigenetic changes such as hypomethylation of *ACE2*, *NF-κB*, and cytokine genes, resulting in increased expression of these genes. On the other hand, the elevated expression of the ACE2 enzyme can increase the pathogenicity of the virus and lead to more oxidative stress in the patient's cells. In addition to the fact that oxidative stress itself can cause mutations and cancer, it can also stimulate the expression of cytokines, especially nuclear factor-kappa B (NF-κB) [13].

Basaran et al. reported that SARS-CoV-2 causes an increase in oxidative stress parameters, DNA damage, and cytokine levels [14]. On the other hand, SARS-CoV-2 induces a cytokine storm and elevates the levels of inflammatory cytokines, including NF-κB [13]. Excessive expression of NF-κB can potentially initiate and promote cancer by stimulating proliferation and metastasis while preventing apoptosis of the cells [15].

Moreover, NF-κB is involved in the generation and maintenance of cancer stem cells (CSCs), which are considered key contributors to tumor initiation, invasiveness, metastasis, and cancer recurrence [16-19]. It should be noted that the activation of NF-κB via SARS-CoV-2 occurs through multiple mechanisms, such as by ORF3a, TLR2-dependent activation, NSP5, and the cytokine storm, which includes an increase in Interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α). However, this activation is typically acute and transient, differing from

the chronic NF-κB signaling observed in cancer, which persists over months or years, and is involved with oncogenic pathways [20-23]. The nucleocapsid protein of SARS-CoV-2 can also activate the expression of cyclooxygenase-2 (COX-2) by binding directly to the regulatory elements of NF-κB [24]. Excessive COX-2 can inhibit apoptosis and stimulate angiogenesis and tumor invasion [25]. COX-2 overexpression in chronic inflammatory conditions, such as *Helicobacter pylori*-induced gastritis or Barrett's esophagus, is well established to be associated with carcinogenesis through the induction of prostaglandin-mediated cell proliferation, angiogenesis, and apoptosis suppression [26, 27]. In most SARS-CoV-2 cases, however, the infection resolves within weeks, although a subset of individuals may experience persistent low-grade inflammation and dysregulation of the immune system [28].

Another signaling pathway that can be affected by SARS-CoV-2 is P38 mitogen-activated protein kinase (MAPK), which is involved in cell differentiation, proliferation, survival, and apoptosis [29-31]. This signaling pathway can be strongly activated by stress and inflammatory cytokines produced by the virus. The p38 MAPK pathway is associated with oncogenesis and cancer cell survival [32, 33] by affecting downstream target molecules, including COX-2, MMP-9, and the epithelial-mesenchymal transition (EMT) process [34, 35]. Notably, these factors are upregulated in severe COVID-19 cases and may contribute to cancer progression by promoting inflammatory microenvironments and affecting tissue remodeling and metastatic factors [36, 37]. It should also be noted that some studies consider this signaling pathway to act as a tumor suppressor gene [38]; therefore, this signaling can have a dual role in cancer. In the case of SARS-CoV-2 infection, it is important to clarify which function of the signaling pathway is more active. To accurately address the precise interaction between viral proteins and oncogenic signaling pathways, we need integrative modeling with computational approaches.

Conclusion

Recently, SARS-CoV-2, which has become a global pandemic, has caused serious problems in global health systems. All researchers are working to stop the initial complications of the virus and reduce mortality. However, it can have a long-term effect on the infected cells by changing the host cells' epigenetic and signaling pathways. Considering that the role of different viruses in the development of different cancers has been proven, one of the possible consequences of SARS-CoV-2 infection could be the development of cancer cells. In this hypothetical paper, we tried to address the potential underlying mechanisms that can be involved in the carcinogenicity of SARS-CoV-2; however, long-term follow-up studies are required to confirm this hypothesis. In this study, the role of SARS-CoV-2 infection in the induction of oncogenic pathways, particularly through viral proteins, such as NSP15 and nucleocapsid, in critical host signaling networks (NF-κB, COX-2, and p38 MAPK) was discussed. However, while the insufficiency of acute infection to directly initiate tumorigenesis has been demonstrated, prolonged inflammation or immune dysregulation could lead to cancer progression. To further advance these observations, we recommend further longitudinal clinical studies to monitor cancer incidence in COVID-19 survivors.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors contribution's

All authors contributed equally to the conception and design of the study, data collection and analysis, interception of the results and drafting of the manuscript. Each author approved the final version of the manuscript for submission.

Conflict of interest

The authors declared no conflict of interests.

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