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COMMENT

Cancer therapy with decreased SARS-CoV-2 infection rates in cancer patients

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SUMMARY

The mammalian target of the rapamycin (mTOR) pathway has been demonstrated to be modulated by numerous RNA viruses. Recent evidence points toward modulation of mTOR in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Patients with cancer, who receive antineoplastic agents that suppress the mTOR/phosphoinositide 3-kinase (PI3K) signaling pathway, may have lower SARS-CoV-2 infection rates and coronavirus disease 2019 (COVID-19) severity.

COVID-19 pandemic urgently warranted the necessity to develop novel therapies against SARS-CoV-2 infection. The mammalian target of the rapamycin (mTOR) pathway has been demonstrated to be modulated in numerous RNA virus infections. Frequently. However, inhibiting mTOR results in the suppression of viral growth and replication. Recent scientific evidence points toward the modulation of mTOR in SARS-CoV-2 infection.

Foote et al. reported that according to the signatures database, 91 antineoplastic agents were associated with downregulation of the gene coding for angiotensin-converting enzyme 2 (ACE2), the entry receptor for SARS-CoV-2. These agents include mTOR/phosphoinositide 3-kinase (PI3K) inhibitors and antimetabolites [1]. Antineoplastic agents, such as mTOR/PI3K inhibitors and antimetabolites, that inhibit the expression of *ACE2* might exhibit clinical anti-SARS-CoV-2 activity [1]. Patients who received antitumor agents that could lower ACE2 showed a statistically significantly reduced SARS-CoV-2 positive rate of 7.0% compared to 12.9% of patients who received other antitumor treatments [1].

Li et al. demonstrated the Middle East respiratory syndrome coronavirus (MERS-CoV) receptor dipeptidyl peptidase-4 (DPP4; CD26), a well-known diabetes-related factor, as a candidate binding target of the SARS-CoV-2 spike protein [2]. Both MERS-CoV and SARS-CoV-2 recognize and bind strongly to the cell receptors, DDP4 and ACE2, respectively, and efficiently infect both bronchial and bronchiole epithelial cells that are not protected by mucus barrier [3].

Remarkably, by 24 h time point after MERS-CoV infection, most of the activated signaling pathways were reported to be associated with cell junctions, e.g. adherens junction pathways, etc., wingless-type MMTV integration site family (Wnt), transforming growth factor (TGF) or PI3K/protein kinase B (AKT)/mTOR inducible signaling pathways, with the suppression of multiple innate immune response-related signaling pathways [4]. A Study of the activated signaling responses at all time points revealed that MERS-CoV infection regulates a broad range of cellular functions, including the PI3K/AKT/mTOR signaling pathways [4].

Of particular interest in the SARS-CoV-2 life cycle is its modulation of the mTOR molecule and its pathways. Importantly, the mTOR signaling pathway is necessary for viral translation during the SARS-CoV-2 life cycle [5]. To ensure the replication of coronavirus, SARS-CoV-2 infection reportedly causes activation of mTOR/PI3K signals. Hepatocyte Nuclear Factor 1 (HNF1) family, which is not included in the mTOR/PI3K signaling pathway, markedly induces the expression of *ACE2* gene [6, 7]. Presumably, mTOR/PI3K signal activation may be a change in cellular function that occurs after SARS-CoV-2 infection rather than inducing *ACE2* gene expression. Therefore, it seems that the rates of SARS-CoV-2 positivity and the attendant severity of COVID-19 will be lower in cancer patients who received antineoplastic agents that suppress the mTOR/PI3K signaling pathway as compared to cancer patients administered other antineoplastic agents (Fig. 1).

Recent studies have shown that a subset of the approved kinase inhibitors targeting the extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) and PI3K/AKT/mTOR pathways significantly inhibited coronavirus replication, including SARS-CoV-2, whether they were administered before or after the viral infection was established. In clinical settings, mTOR/PI3K inhibitors (everolimus, temsirolimus and alpelisib), other kinase inhibitors (dasatinib and crizotinib) and antimetabolites (decitabine and gemcitabine) are prescribed as antineoplastic agents to patients with cancer. Thus, antineoplastic agents inhibiting the activity of ERK/MAPK or PI3K/AKT/mTOR are not only suppressing malignant tumour growth but also mitigating the severity of cancer patients with SARS-CoV-2 infection by inhibiting SARS-CoV-2 replication (Fig. 1). Patients with cancer who received antineoplastic agents that inhibit the mTOR/PI3K signaling pathway might exhibit a statistically significant reduction in SARS-CoV-2 positivity rates and correspondingly lower rates of COVID-19 severity. Taken together, from the perspective of preventing the severity of COVID-19 and treating cancer patients infected with SARS-CoV-2, it is important to consider the therapeutic effects of mTOR inhibitors, other kinase inhibitors, or DPP4 inhibitors because of their inhibitory properties on the mTOR/PI3K signaling pathway.

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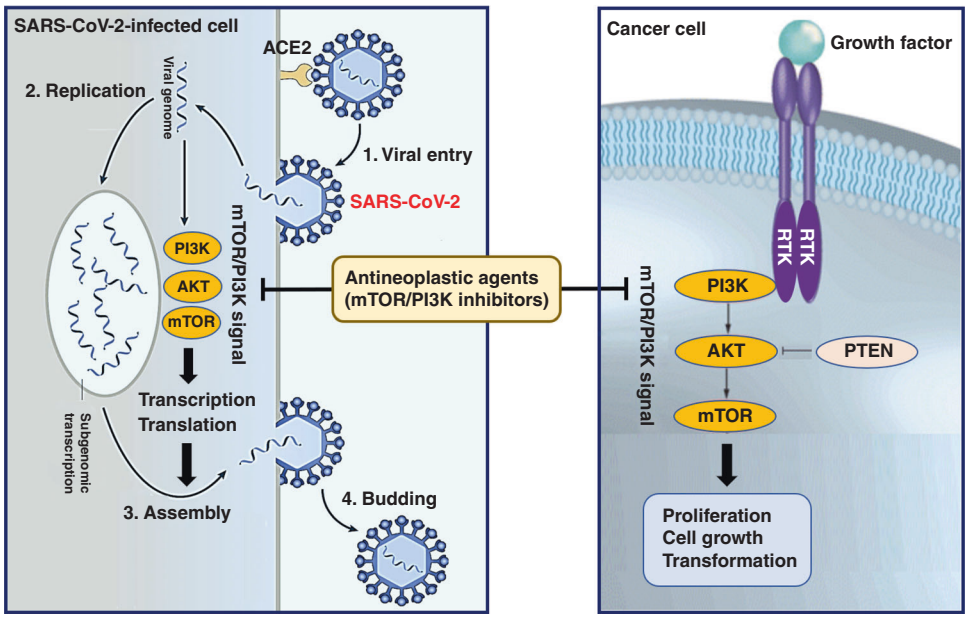

Fig. 1 Antiviral effect of antineoplastic agents inhibiting mTOR/PI3K signaling pathway in SARS-CoV-2 infection in cancer patients. Activation of the mTOR/PI3K signaling pathway in the host cell contributes to the viral life cycle from gene transcription to mRNA translation into proteins and subsequent assembly/budding of SARS-CoV-2. Additionally, mTOR/PI3K signaling pathway promotes replication and proliferation of cancer cells. Therefore, antineoplastic agents that inhibit the mTOR/PI3K pathway does not only suppress the growth of cancer cells but also inhibit the replication of SARS-CoV-2. AKT protein kinase B-alpha, mTOR mammalian target of rapamycin, PI3K phosphoinositide 3-kinase, RTK receptor tyrosine kinase, SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

Disclaimer

The material (manuscript and figure) is original research. It has not been previously published and has not been submitted for publication elsewhere while under consideration.

DATA AVAILABILITY

This manuscript is an editorial and does not contain research data. Therefore, there is no research data or information to be published or opened.

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AUTHOR CONTRIBUTIONS

TH wrote the manuscript. IK carefully reviewed the manuscript and commented on aspects of clinical medicine. IK shared information on clinical medicine and oversaw the entirety of the study.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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