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Review Article

The Oncolytic Viral Activity of SARS-CoV-2

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Abstract

The expanding domain of biotechnology has fostered the development of genetically modified viruses as pivotal players in advanced therapeutic strategies. Among these, oncolytic virus (OV) therapy has emerged as a promising avenue in cancer treatment. This review explores the feasibility and potential mechanisms underlying the utilization of a genetically engineered SARS-CoV-2 variant as an oncolytic agent. We propose that a modified SARS-CoV-2, engineered for reduced virulence, could be employed as a therapeutic tool against cancer. Mechanistically, upon infection, SARS-CoV-2 can activate the immune system, triggering an anti-tumor response through various pathways such as NK cell activation, molecular mimicry, and viral entry via ACE-2/NRP-1 receptors. Additionally, the downregulation of inhibitory molecules on NK cells post-infection further enhances anti-tumor activity. We elucidate the process of engineering modified SARS-CoV-2 utilizing a reverse genetic system, highlighting the safety measures necessary for its preparation. Moreover, we discuss strategies for retargeting coronavirus to enhance oncolytic efficacy, focusing on modifications to viral surface proteins. Clinical evidence supporting the potential of SARS-CoV-2-induced tumor regression is presented, including cases of spontaneous remission following COVID-19 infection or vaccination. These observations underscore the need for further investigation into the immunological mechanisms driving tumor regression post-SARS-CoV-2 infection. In conclusion, harnessing the therapeutic potential of genetically modified SARS-CoV-2 as an oncolytic virus represents a promising frontier in cancer therapy. By elucidating the underlying mechanisms and leveraging novel biological treatments, such as immune checkpoint inhibitors, may lead to tailored and effective cancer treatments with reduced side effects.

***Keywords:** SARS-CoV-2; Oncolytic virus; Cancer therapy; Biotechnology; ACE-2/NRP-1.*

1. Introduction

As the field of biotechnology expands, genetically modified viruses have become crucial components of advanced therapeutic approaches [1]. Medical researchers have manipulated viruses' capacity to enter cells and transport viral information by using genetic engineering to deliver genes to cure genetic illnesses. This is known as virotherapy [2]. An innovative approach to treating cancer is called oncolytic virus (OV) therapy. Oncolytic virus (OV) is a biologically effective preparation that can enter the body to play a part via an intravenous drip, intratumor injection, intraspinal drip, and other methods of administration. Numerous weakly pathogenic wild-type and genetically altered viruses that preferentially reproduce in and particularly kill cancer cells are involved. Several OVs, including rhabdoviruses like Marabi, vesicular stomatitis virus (VSV), and Coronavirus, have demonstrated positive anticancer effects in preclinical and clinical contexts. OV can treat both solid and non-solid tumors. OVs can be activating the host's anti-tumor immune system and recruit more effector lymphocytes in the tumor microenvironment to kill tumor cells, as illustrated in Fig. 1.

Because of the rapid progress of reverse genetic manipulation technology, gene edited OVs have a wide range of applications. Amgen, an American pharmaceutical company, developed a gene-edited attenuated HSV-1 that can be injected into the tumor to treat unresectable melanoma that recurs after surgery, and it was authorized by the US Food and Drug Administration in 2015. This is the first time OV treatment has been used. Given the virus's favorable anti-tumor efficacy in clinical studies, phase 3 clinical trials with PD-1 antagonists have been conducted. Biotechnology has accelerated the advancement of OV research and deepened people's knowledge of OV and tumor molecular mechanisms [3].

2. Proposed genetically modified SARS-CoV-2 as an Oncolytic Virus:

We suggest that a genetically altered SARS-CoV-2, with dramatically reduced virulence, could be used to infect a cancer patient as a kind of therapy. Depending on the impending malignancy, this treatment strategy may follow either the upregulation or the downregulation pathways of NK cells. A patient can also become infected with SARS-CoV-2, a lytic virus that is known to release its contents, including DNA, ribosomes, proteins, and numerous organelles, causing the immune system to become activated and start attacking the cancerous cells via tumor-associated antigens.

Although this suggestion may seem contentious, it may be useful for individuals with terminal neoplastic disorders who have a dismal prognosis and against whom traditional treatments have little to no effect. Numerous antigens are generated during a cytokine storm, and these antigens may encourage interactions between viral proteins and tissue-specific neoplasms, which could lead to the virus's effective reproduction. Dendritic cells, macrophages, and B cells would present antigens to the body more frequently as a result. Cytokine production can also aid in the activation of NK cells. Through the expression of specific genes, such as LAG-3, which controls the regulation of worn-out cytotoxic T cells, such an environment would allow for the upregulation and reactivation of tired CD8+T cells.

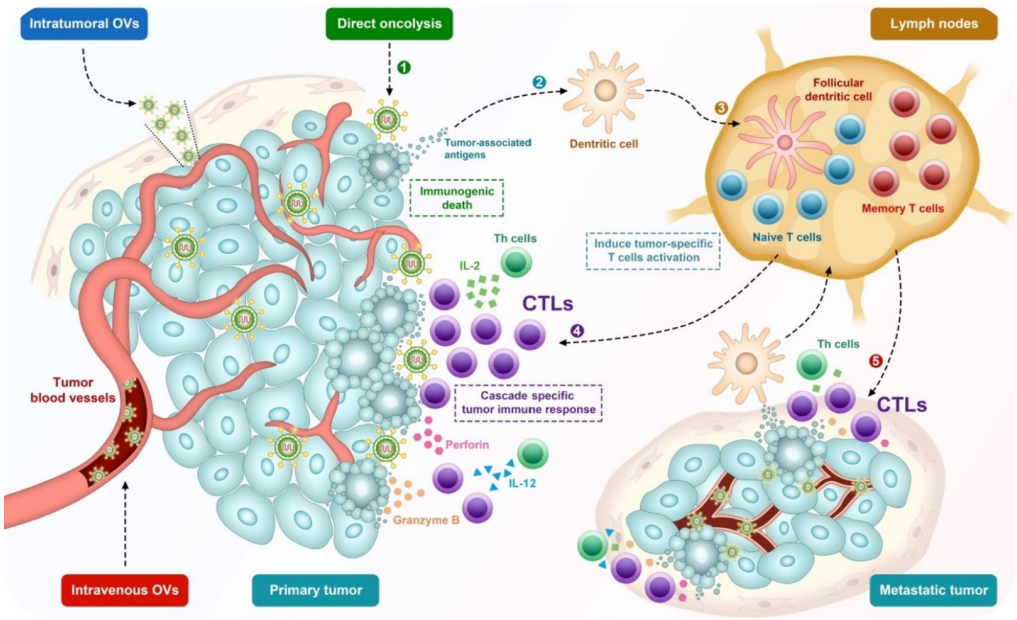

Figure 1. *Shows diagram of an oncolytic virus's anticancer process. OVs can reach the tumor site through a variety of routes. (Such as intratumorally injection or intravenous injection). Oncolytic viruses that enter the tumor site can cause immunogenic death of tumor cells via direct oncolysis (1), release a variety of tumor-associated antigens after being taken up by DC (2), enter the lymph nodes via lymphatic reflux, present tumor antigen information to naive T cells in the lymph nodes, induce differentiation to produce tumor-specific effector T cells (3), and activate the tumor immune response. With ongoing oncolysis and T cell-specific immune assault, more tumor-associated antigens are released, and more effector T cells are generated via DC presentation, resulting in a cascade of specific tumor immune responses (4). Furthermore, memory T cells found in lymph nodes or tumor inflammation sites will perform immune tracking of distant tumors, differentiate into effector T cells capable of killing tumor cells, and decrease malignant metastasis and recurrence (5). [3]*

Among the effector activities of CD8+ T cells are the release of IL-2 (which recruits NK cells) and interferon-gamma (which inhibits tumor proliferation and angiogenesis). Unfortunately, predicting which cytokines will be produced in what amounts is difficult because it all depends on the uniqueness of one's immune response, but a common denominator that must be addressed in this therapy suggestion is the management of IL-6 as well as the inhibition of PD-L1. IL-6 is a proinflammatory cytokine having pleiotropic biological activities that include the induction and maintenance of B cell regulation and Th17 cell development, as well as other actions associated with acute inflammation, such as the induction of acute-phase reactant production by the liver. Because IL-6 is known to cause the most damaging effects of the COVID-19 cytokine storm, as well as to inhibit lymphocyte recruitment and development, its inhibition has been proposed as a therapeutic therapy, particularly for patients with severe infection.

Furthermore, IL-6 promotes tumor formation, progression, and dissemination by inducing angiogenesis and intracellular adhesion molecules. PDL-1 is present on the cell surface of many aggressive neoplasms and is a critical role in inducing T-cell exhaustion. As a result, the combination of IL-6 blockers as well as a PD-L1 inhibitor could be effective in cancer treatment when earlier testing for PD-L1 expression on tumor resident cells has been proven, ensuring that the inhibitor has a true effect. This is critical since PDL-1 inhibitors might have significant autoimmune adverse effects. The combination of treatments may help reduce the emergence of side effects previously linked to these biologics by lowering the required dosage of PDL-1 and IL-6 inhibitors. We believe that a "controlled" infection with a modified variant of SARS -CoV-2, combined with the administration of IL-6 blockers and PD-L1 checkpoint inhibitors, can induce the regression of certain difficult-to-treat aggressive cancers [1].

3. Preparation of engineering-modified SARS-CoV-2 using a reverse genetic system

The first stage of the process involves preparing the seven plasmids containing SARS-CoV-2 fragments F1-F7. Before assembling the full-length SARS-CoV-2 DNA, the plasmids should be verified using restriction enzyme digestion and Sanger sequencing to rule out the introduction of any unwanted mutations. Stage 2 includes the digestion of the Maxiprep plasmids with restriction enzymes to produce high-quality DNA fragments for downstream experiments. In Stage 3, the seven DNA segments are assembled in vitro into a full-length SARS-CoV-2 DNA using a T4 DNA ligase. Two distinct ligation stages boost the ligation efficiency of the full-length DNA while avoiding nonspecific ligation between fragments F3 and F7.

Following that, the full-length ligation product is purified instantly using phenol-chloroform extraction and isopropanol precipitation. In vitro production of full-length RNA and N gene RNA occurs in Stage 4. The SARS-CoV-2 recombinant virus is recovered from cell growth in Stage 5 using RNA electroporation. Electroporation can be accomplished using either Vero E6 cells only or BHK-21 and VeroE6 cells. Stage 6 entails whole genome Sanger sequencing of the virus to confirm the viral genome structure, as illustrated in Fig. 2. Stages 1-4 procedures can be carried out in a standard laboratory. Stages 5 and 6 processes that involve manipulating the SARS-CoV-2 must be carried out in a biosafety laboratory level 3 (BSL-3) facility [4].

4. Retargeting of Coronavirus to Generate Oncolytic Agents

4.1 Modification of Viral Surface Proteins

The spike (S) protein oversees binding to receptors and later cell entry via virus-cell membrane fusion. The amino terminal S1 domain is necessary for virus binding to cells, and the S2 domain mediates fusion with the cell membrane while enduring ordered structural changes, so transduction targeting via virus surface protein modification is illustrated in Fig. 3. Coronavirus infection of cells is dependent on the expression of specific cellular receptors, making these viruses extremely species-specific [5].

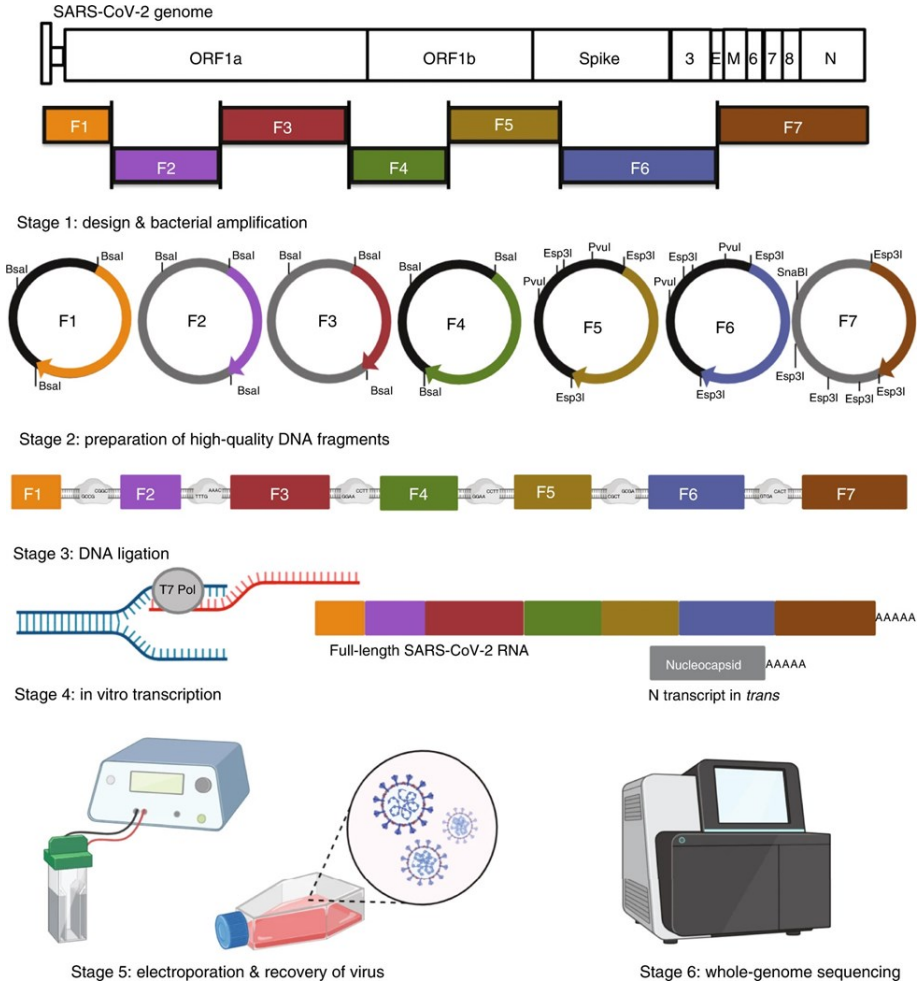

Figure 2. *Shows an overview of SARS-CoV-2 reverse genetic system. The SARS-CoV-2 infectious clone model contains seven cDNA fragments to cover the complete viral genome, to disrupt toxic elements, and to aid in genetic manipulation. The SARS-CoV-2 plasmids are amplified in E. coli and sequentially ligated following digestion with type II restriction enzymes to remove the plasmid backbone. The full-length viral DNA is then in vitro transcribed using T7 polymerase to generate full-length genomic SARS-CoV-2 RNA and electroporated into cells with N-protein transcript expressed in trans. Following electroporation, cells are seeded into cell culture flasks and virus recovered 2–5 d post electroporation [4].*

5. The mechanisms described in cases of observed tumor regression by SARS-CoV-2:

5.1 NK Cell Activation in Response to SARS-CoV-2

This mechanism was proven in a case report of a pituitary microadenoma spontaneously resolving as a result of an immune response to COVID-19. It has been hypothesized that when patients have an infectious process, such as COVID-19, in the presence of a cancer diagnosis, a scenario is created in which the virus's excessive inflammatory response eventually overwrites the primary tolerant environment of the innate immune system, resulting in spontaneous resolution of the tumor. Evidence of such an antitumor response has previously been recorded in the context of infectious processes (pneumonia and Clostridium difficile colitis) preceding COVID-19, which resulted in the spontaneous regression of a diffuse large B-cell lymphoma of the maxillary sinus [1, 6, 7].

Another case report found that SARS-CoV-2 induced an antitumor immune response, resulting in the remission of a stage III Hodgkin lymphoma via cross-reactivity of viral-specific T cells with tumor antigens, as well as natural killer cell activation by inflammatory cytokines produced in response to the SARS CoV-2 infection. Figure 4 illustrates this process.

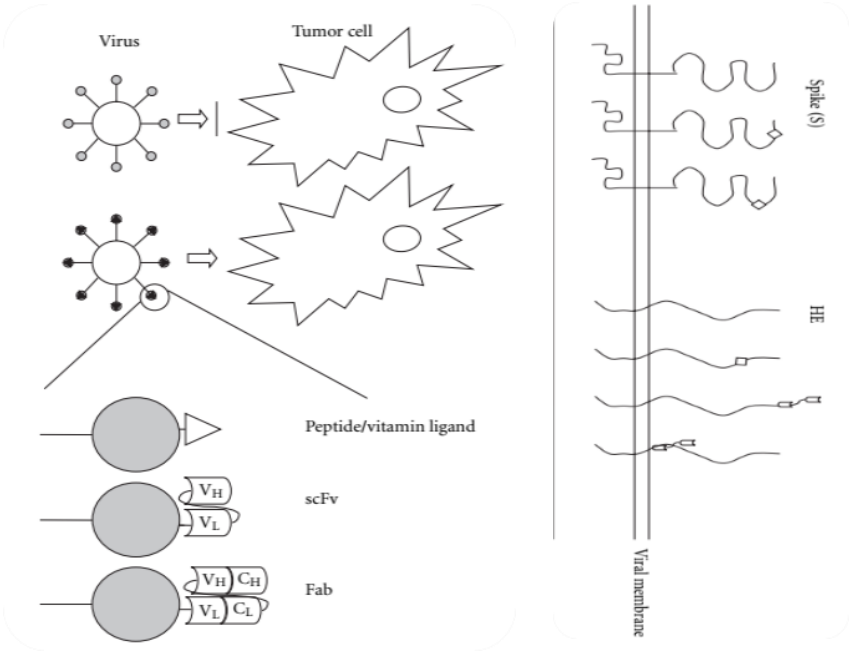

Figure 3. *Shows transduction targeting via virus surface protein modification. Principle of virus redirection by inserting tumor-specific ligands into the viral coat; no infection without modification of viral surface protein (upper part); Schematic representation of a viral surface protein (represented by the grey-filled circle) on which tumor-binding peptides or antibodies are exposed. Ligands can be introduced at the N- or C-terminus of the protein or internally if the viral protein's proper folding and accessibility for binding to the cell surface receptor are preserved. Modification of viral surface proteins for coronavirus redirection to tumor cells. The surface glycoproteins spike (S) and hemagglutinin esterase (HE), as well as the modifications used to direct the virus to new target cell antigens, are depicted schematically [5].*

A third case report, not linked with an infection but with the administration of an mRNA vaccine for COVID-19, mentioned the same activating mechanism. In this case, the authors showed that after the second vaccination boost, a patient with a previous myoepithelial cancer of the left parotid gland and lung metastasis had a 50% to 73% reduction in lung metastasis after 9 months, with no additional treatment. The tumor immune microenvironment was analyzed using mass cytometry before and after vaccination, revealing significant immunological changes, most notably the infiltration of T cells and NK cells, which, in contrast to pre-vaccination samples, demonstrated infiltration with M2 macrophages and neutrophils; importantly, M2 macrophages are associated with the tolerant state that promotes tumor growth [1].

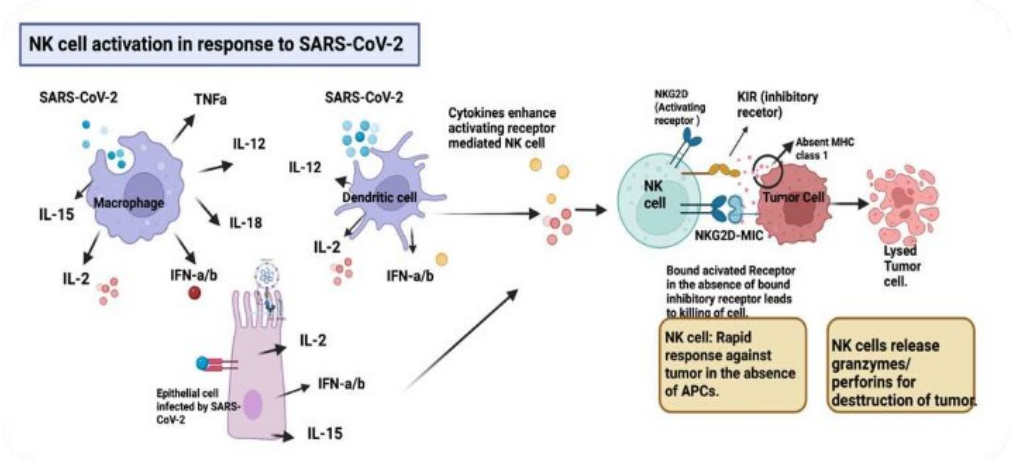

Figure 4. *Shows inflammatory cytokines such as IL-12, IL-15, IL-2, IFN-, and INF- produced in response to SARS-CoV-2 by various cells such as macrophages, dendritic, and epithelial lung cells upregulate the expression of activating receptors (NKG2D) in NK cells, promoting a rapid response against tumor cells in the absence of APCs. Tumor cells use downregulation of MHC class I presentation as an evasion strategy, which activates NK cells. When activated, NK cells produce granzymes and perforins that kill the tumor. BioRender.com was used to create this [1].*

5.2 Molecular Mimicry or Cross-Reactivity

Another possible mechanism for tumor regression, states that molecular mimicry may play an essential part in tumor reduction and remission. SARS-CoV-2 proteins, including the Spike protein, are mimicked by tumor cell surface markers such as heat shock proteins (HSP60, HSP70), eliciting a similar immune reaction. This method of cross-reactivity could enable cytotoxic T cells and antibodies produced specifically against the virus to target cancer cells, resulting in tumor regression [1, 2, 8].

However, there is still a missing link because, often, antigen mimicry is insufficient, and the addition of danger signals, which typically represent the result of a true tissular insult, is required for the development of a complete and robust immune response. Because the insult becomes real in the setting of COVID-19, this proposed mechanism following acute infection may be adequate for DCs to promote T-cell activation. In terms of changes in the microenvironment, the development of bystander activation may be the route that renders cells more susceptible to activation. To develop a true strategy for innovative treatments, the characterization of such danger signals in the context of tumor-elicited immune responses needs to be further explored [1].

5.3 SARS-CoV-2 Viral Entry through ACE-2/NRP-1 following Destruction by Cytotoxic T Cells

A different mechanism was reported in a case series of three patients with metastatic colorectal cancer who showed evidence of tumor reduction in the presence of COVID-19. SARS-CoV-2 infects cells via an association of the receptor binding domain (RBD) in the spike (S) protein with the human receptor ACE-2. Although ACE-2 receptors are frequently found in alveolar pneumocytes, they have also been found in other tissues, enabling infection of other types of cells, including colon cells. The interaction between SARS-CoV-2 and colon cancer cells was hypothesized to occur via a previously known mechanism, which most likely guides SARS-CoV-2 infectivity pleiotropism and consists of an interaction between the S1 protein and the transmembrane receptor neuropilin-1. (NRP-1). Interestingly, co-expression of ACE2 and NRP1 on a human colon cancer cell line (Caco-2) increased infectivity when compared to cells expressing only the ACE2 receptor.

Tumor reduction in these instances could be explained by SARS-CoV-2 interacting with colon cancer cells via the ACE-2/NRP-1 receptors. The interaction between the virus and the colon cancer cells is directed by the presence of the complex ACE2/NRP-1, allowing for an easy infection and eventually leading to a direct immune response and tumor cell destruction by cytotoxic T cells. In this respect, the presence of ACE2 receptors and NRP-1 in various tissues could be viewed as a prognostic marker in patients with specific cancer types and in favor of using SARS-CoV-2 as an oncolytic agent. Figure 5 shows a more detailed schematic depiction of this mechanism [1].

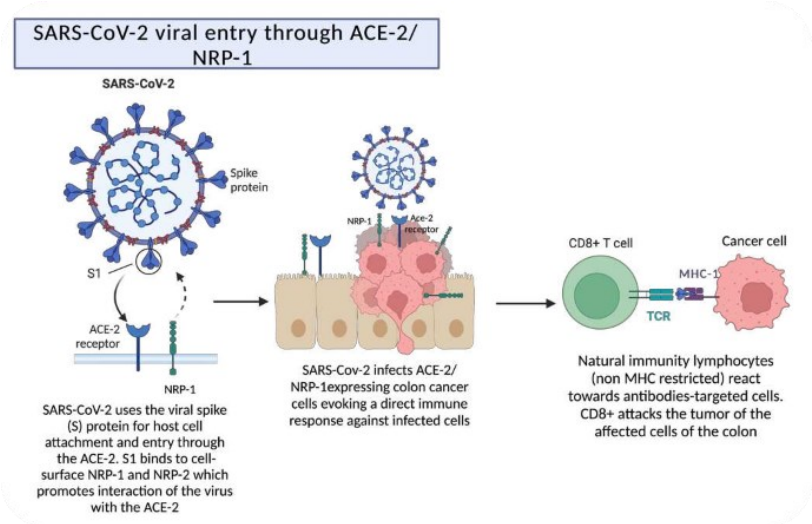

Figure 5. *Shows the interplay of SARS-CoV-2 and ACE-2/NRP-1 receptors reduce tumor growth. ACE-2 receptors are found in alveolar pneumocytes and other tissues, allowing the virus to enter and adhere. The presence of the coreceptor neuropilin-1 promotes virus interaction with the ACE-2 receptor, resulting in a direct immune reaction. BioRender.com was used to create this [1].*

5.4 Downregulation of NK Cells via the Expression of Inhibitory Molecules after Infection by SARS-CoV-2 through the ACE2 Receptor

Downregulation is another mechanism that should be investigated further to cause the reduction/remission of certain neoplasms. In deranged hematological malignancies like NK lymphomas, neoplastic cells evolve evasion mechanisms that prevent the host's immune response from being directly targeted by CD8+ T cells. However, neoplastic NK cells express a variety of inhibitory substances that can be downregulated. SARS-CoV-2 was able to infect both healthy and neoplastic NK cells via the ACE2 receptor and then induce the expression of the inhibitory receptor NKG2A in large quantities, leading to exhaustion, a reduction in cytotoxic activity, and even the induction of apoptosis in the NK lymphoma remission case report (Figure 6).

Because of the large number of receptors that NK cells can express on their surface, they are excellent prospects for rapid upregulation as well as downregulation. The HLA-E ligand almost always activates the NKG2 receptor family, and this mechanism can take two forms: activation via NKG2C/E/D, particularly NKG2D, or deactivation via NKG2A, as previously stated. The Ly49 membrane receptor family is also implicated in the activation or inhibition of NK cells, particularly in antiviral and antitumor states. The KIR (Killer cell Immunoglobulin-like Receptor) family can also trigger both upregulation and downregulation pathways [1, 9, 10].

Because of the speed with which NK cells can elicit antitumor immunity, it is critical to investigate mechanisms involving SARS CoV-2 as a stimulator of tissue-specific cytokines to activate NK cells and promote their infiltration of tumor niches (which can sometimes be inaccessible to cytotoxic drugs) to eradicate cancer cells. Another case report of a complete recovery of a follicular cell lymphoma in the presence of COVID-19 demonstrated the shrinkage of a para-aortic lymph node. This evidence supports the theory that an important inflammatory process could reactivate the immune system. Although it was observed that an immune response was elicited following SARSCoV-2 infection, resulting in the partial destruction of the tumor, there was no distinct description of the molecular/immunological mechanisms leading to its remission [1].

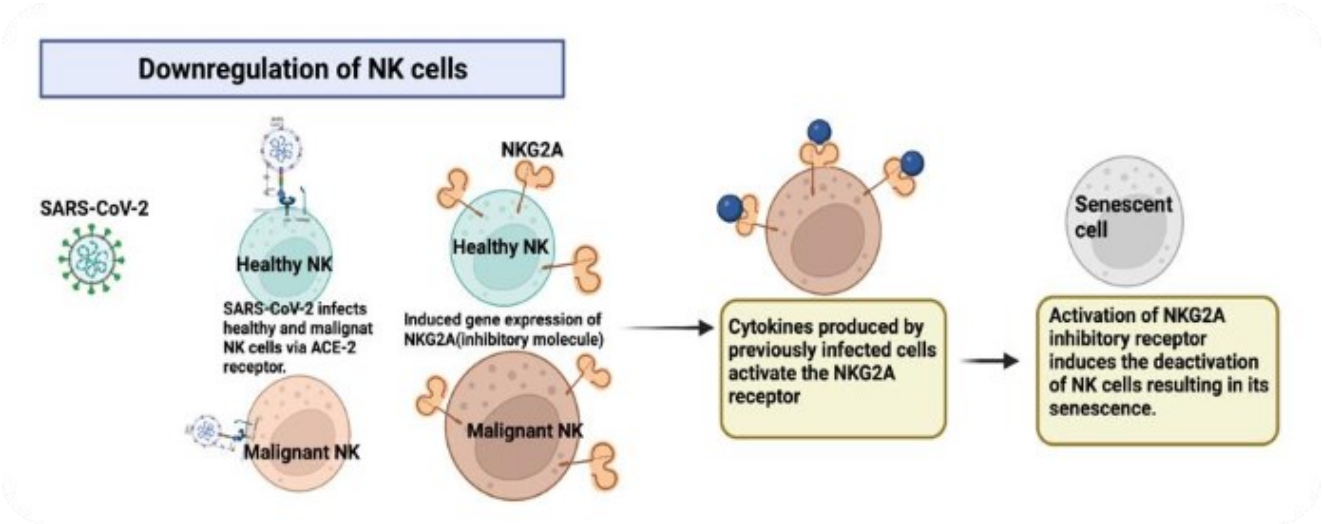

Figure 6. *Shows SARS-CoV-2 infects both healthy and malignant NK cells, inducing cell senescence by increasing the expression of the inhibitory molecule NKG2A. BioRender.com was used to create this [1].*

Table 1. Shows Case Reports and Case Series of patients with remission after SARS-CoV-2 exposure [1, 11, 12, 13].

Cancer diagnosis before infection by SARS-CoV-2	Clinical Evaluation after SARS-CoV-2 infection
A 57-year-old lady was diagnosed with acute myeloid leukemia M2 with a 11q23/KMT2A abnormality.	Blood cell counts returned to normal two months after the original diagnosis and infection. A re-evaluation of leukemia showed normocellular marrow with 55% cellularity and less than 5% blasts. Final diagnosis: spontaneous morphologic remission in the absence of disease-modifying treatment for acute leukemia. One month later, the FISH analysis showed a normal result, proving the molecular cytogenetic remission. The patient developed a hematological recurrence of the primary illness eight months later.
A 20-year-old man was diagnosed with relapsed/ refractory NK/T cell lymphoma, Epstein-Barr virus, and autoimmune hemolytic anemia.	The patient appeared with a spontaneous steady clinical improvement, with hemolytic markers and platelet count normalization, eleven days after the start of SARS-CoV-2. Reduced the amount of both healthy and malignant NK clonal cells while increasing the number of CD8+ T cells. Plasma EVB-DNA levels were reduced from 229,876 copies/mL to 495 copies/mL. Final diagnosis: NK lymphoma remission during SARS-CoV-2 illness. A recurrence of SARS-CoV-2 infection was discovered two months after the initial outbreak.
T2NOMX metastatic myoepithelial carcinoma of the left parotid gland in a 61-year-old lady.	CT scans revealed evidence of persistent tumor shrinkage: 50%, 67%, and 73% reductions at 3, 6, and 9 months after the second dosage of the SARS-CoV-2 vaccine, respectively.
A 32-year-old male with pituitary microadenoma, secondary adrenal insufficiency, and scotoma was treated with steroids for two years.	Three months after the SARS-CoV-2 infection was resolved, the patient experienced a control MRI, which revealed improvement in the pituitary microadenoma. The changes included the disappearance of the prior MRI's hypointense lesion and hyperintense enhancement. (6 months before). Clinically, the patients' blurry eyesight and headaches improved.

Conclusions

In summary, this review explores the prospect of utilizing genetically modified SARS-CoV-2 as an oncolytic virus, shedding light on its mechanisms and clinical implications in cancer therapy. Key findings suggest that SARS-CoV-2 infection can induce anti-tumor responses through various immune-mediated pathways, offering a novel approach to cancer treatment.

However, several unresolved issues warrant further investigation. Firstly, the precise mechanisms underlying SARS-CoV-2-induced tumor regression remain incompletely understood, necessitating additional research to elucidate these processes. Additionally, the safety and efficacy of engineered SARS-CoV-2 variants as oncolytic agents require rigorous evaluation in preclinical and clinical settings.

Moving forward, future directions for research in this field include elucidating the immunological mechanisms driving tumor regression post-SARS-CoV-2 infection, optimizing the engineering of modified SARS-CoV-2 variants for enhanced oncolytic efficacy, and conducting comprehensive clinical trials to assess their therapeutic potential in diverse cancer types.

Overall, the exploration of genetically modified SARS-CoV-2 as an oncolytic virus presents exciting opportunities for advancing cancer therapy. By addressing unresolved issues and pursuing potential future directions, this review lays the groundwork for the development of innovative and effective treatments for malignancies resistant to traditional therapies.

Conflict of Interest

The authors declare no conflict of interest.

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