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REVIEW

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Oncogenic potential of SARS-CoV-2—targeting hallmarks of cancer pathways

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Abstract

The 2019 outbreak of SARS-CoV-2 has caused a major worldwide health crisis with high rates of morbidity and death. Interestingly, it has also been linked to cancer, which begs the issue of whether it plays a role in carcinogenesis. Recent studies have revealed various mechanisms by which SARS-CoV-2 can influence oncogenic pathways, potentially promoting cancer development. The virus encodes several proteins that alter key signaling pathways associated with cancer hallmarks. Unlike classical oncogenic viruses, which transform cells through viral oncogenes or by activating host oncogenes, SARS-CoV-2 appears to promote tumorigenesis by inhibiting tumor suppressor genes and pathways while activating survival, proliferation, and inflammation-associated signaling cascades. Bioinformatic analyses and experimental studies have identified numerous interactions between SARS-CoV-2 proteins and cellular components involved in cancer-related processes. This review explores the intricate relationship between SARS-CoV-2 infection and cancer, focusing on the regulation of key hallmarks driving initiation, promotion and progression of cancer by viral proteins. By elucidating the underlying mechanisms driving cellular transformation, the potential of SARS-CoV-2 as an oncovirus is highlighted. Comprehending these interplays is essential to enhance our understanding of COVID-19 and cancer biology and further formulating strategies to alleviate SARS-CoV-2 influence on cancer consequences.

Keywords Coronavirus, COVID-19, Cancer hallmarks, Tumorigenesis, Oncovirus

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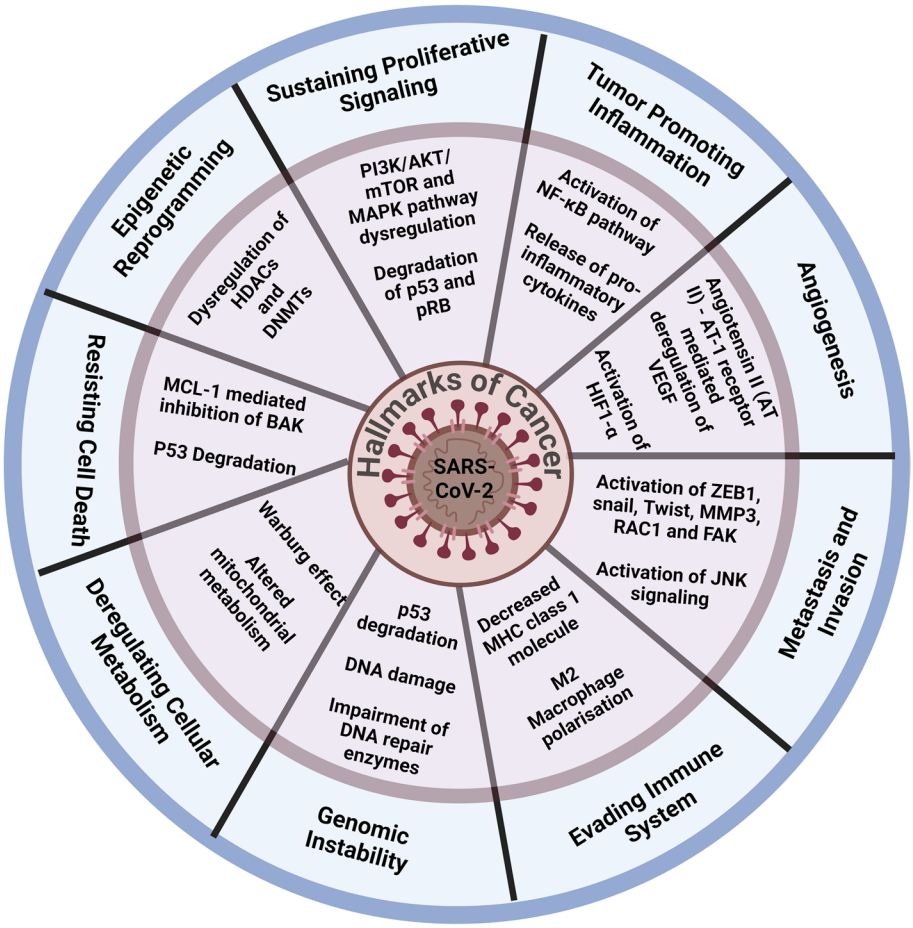
Graphical Abstract

Schematic representation of SARS-CoV-2 associated alterations contributing to various hallmarks of cancer. PI3K/ AKT/ mTOR: Phosphoinositide 3-kinase/Protein Kinase B/ Mammalian Target of Rapamycin; TGF-β, Transforming Growth Factor-beta; VEGF, Vascular Endothelial Growth Factor; JNK, Jun N-terminal Kinase; HDAC, Histone Deacetylase; DNMT, DNA Methyltransferase; HIF-1α: Hypoxia-Inducible Factor 1-alpha; pRB, Retinoblastoma Protein. This image was created using BioRender software.



Introduction

The emergence of SARS-CoV-2 in 2019, leading to the COVID-19 pandemic, has presented a significant global health crisis. As of September 13, 2023, over 770 million confirmed cases and 6.9 million deaths worldwide have highlighted the ongoing challenges posed by COVID-19 [1]. This crisis has resulted in substantial socioeconomic difficulties and an unprecedented healthcare crisis, with a lack of effective treatment exacerbating the situation [2].

Individuals with pre-existing health conditions, including diabetes, obesity, hypertension, and chronic obstructive pulmonary disease (COPD), face an increased risk of severe complications from COVID-19 [3]. For instance, COPD increases the severity of COVID-19, with patients at a 14-fold higher risk compared to those without COPD due to compromised respiratory function. This condition heightens susceptibility to severe respiratory symptoms such as pneumonia and acute respiratory distress syndrome (ARDS) following COVID-19 infection. Cardiovascular diseases, managed with medications like ACE inhibitors and ARBs, may inadvertently facilitate SARS-CoV-2 entry through ACE2 receptors, worsening cardiovascular complications such as myocarditis and acute coronary syndrome. Diabetes mellitus exacerbates COVID-19 severity, leading to prolonged hospitalization and a heightened risk of complications due to elevated blood glucose levels and compromised immune responses. Obesity is yet another risk factor for severe

COVID-19, driven by several interconnected mechanisms. Increased adipose tissue elevates levels of ACE2, facilitating SARS-CoV-2 entry into cells, including adipocytes, which may serve as reservoirs for the virus. Obesity is linked to insulin resistance and increased activity of the renin–angiotensin–aldosterone system, leading to elevated levels of angiotensin II, which in turn worsens lung injury and inflammation. Furthermore, obesity impairs pulmonary function, decreases respiratory efficiency, and is linked to chronic low-grade inflammation, all contributing to worse outcomes in COVID-19 patients. Chronic kidney disease (CKD) predisposes patients to more severe COVID-19 outcomes, likely due to compromised immune function and overall health status, increasing mortality risk, especially in moderate to severe cases. Smoking history significantly increases the severity of COVID-19, possibly due to increased expression of ACE2 receptors in respiratory tissues, making smokers more prone to severe infections and requiring more intensive medical care [4, 5]. Notably, cancer is also a major risk factor underlying covid-19 as existing clinical studies have shown that cancer patients appear to be more susceptible to contracting COVID-19 and experiencing severe complications, with mortality rates twice as high as those among non-cancer patients. Moreover, the impact of COVID-19 on mortality varies based on cancer type and stage, and patients with hematologic, lung cancer and metastatic tumors showing the highest mortality rates [6–8].

Interestingly, the risk factors associated with COVID-19 also contribute to cancer development. COPD and lung cancer are interrelated through shared mechanisms and risk factors, primarily driven by tobacco smoking and air pollution. Chronic inflammation in the lungs from these sources generates reactive nitrogen and oxygen species (RNOS), which can initiate carcinogenesis through DNA damage and mutations. COPD-related mitochondrial dysfunction exacerbates this process by impairing cellular function and increasing oxidative stress. Inflammatory pathways like NF-κB and PI3K, activated in COPD, also play roles in cancer development and progression. The hypoxic conditions in COPD patients activate hypoxia-inducible factor (HIF)-1α, supporting tumor cell survival and growth. The chronic inflammatory milieu in COPD alters the lung microenvironment, further driving carcinogenesis [9, 10]. Obesity is yet another major risk factor that contributes to cancer risk through chronic inflammation and metabolic dysfunction. Excess adipose tissue secretes pro-inflammatory cytokines such as TNF-α and IL-6, promoting an environment conducive to cancer development by stimulating cellular proliferation and inhibiting apoptosis. Obesity also leads to insulin resistance and elevated levels of insulin and insulin-like growth factor-1 (IGF-1), which can enhance tumor growth and increase cancer risk in malignancies such as breast, colorectal, and prostate cancers [11].

Diabetes mellitus, particularly type 2 diabetes, exacerbates cancer risk through similar mechanisms. Elevated blood glucose levels and hyperinsulinemia promote cancer progression by stimulating cell proliferation and survival. Insulin and IGF-1, both elevated in diabetes, act as growth factors that facilitate tumor growth and increase cancer risk in cancers such as pancreatic, liver, and colorectal cancers. The metabolic disturbances associated with diabetes, including increased oxidative stress and inflammation, further elevate cancer risk [12].

Furthermore, Cardiovascular disease (CVD) and chronic kidney disease (CKD) contribute to cancer development through mechanisms involving chronic inflammation, oxidative stress, metabolic disturbances, and hormonal dysregulation. In CVD, inflammation and oxidative stress from conditions like hypertension promote DNA damage and ECM stiffening, creating a pro-tumorigenic environment and enhancing angiogenesis via increased VEGF expression. CKD exacerbates cancer risk through systemic inflammation, immune dysfunction, and accumulation of uremic toxins, which impair the ability of body to eliminate malignant cells. Additionally, markers of kidney function such as eGFR and albuminuria are linked to cancer risk, with metabolic disturbances like insulin resistance and dysregulated RAAS further promoting oncogenesis [13].

Understanding the mechanisms behind the interrelation between these risk factors, COVID-19, and cancer underscores the importance of investigating SARS-CoV-2 as a potential oncovirus. Additionally, recent advancements have revealed potential links between SARS-CoV-2 and cancer, with studies identifying shared factors, such as compromised immune systems and excessive production of pro-inflammatory cytokines contributing to the increased risk of COVID-19 infection in cancer patients [14, 15]. Network analysis studies have identified biological processes and potential oncogenes affected by COVID-19, suggesting implications for cancer development [16–18] Moreover, retrospective case series have highlighted the frequency of certain cancer types among COVID-19 patients, with lung cancer displaying the highest mortality rate [8]. These findings underscore the potential correlation between cancer types and COVID-19 outcomes, necessitating further research to elucidate underlying mechanisms and implications.

In the present review, we discuss the various biological alterations induced by SARS-CoV-2 infection and its proteins with respect to cancer hallmarks.

Furthermore, we examine the shared signaling pathways and molecular modifications that occur during SARS-CoV-2 infection, paralleling the processes observed in the initiation and progression of cancer. We have further sought to unravel the intricate interplay and potential connections between these two complex phenomena.

Computational tools and approaches into SARS-Cov-2 and host protein interactions

Studying the interaction of SARS-CoV-2 proteins with host proteins through in silico approaches using various computational tools has elucidated key genes and molecular interactions between the virus and host. These approaches have identified and characterized the mechanisms of viral infection and its subsequent effects on host cellular pathways. Table 1 summarizes the different computational research and software that have been utilized to analyse the interactions between SARS-CoV-2 proteins and mammalian oncogenes or tumor suppressor proteins, highlighting the hallmarks of cancer and altered signaling pathways involved.

Network analysis using tools like Cytoscape and BiNGO has mapped interactions between SARS-CoV-2 and host proteins, identifying key players such as SRC, MYC, EGFR, c-Jun and c-Fos which are involved in oncogenic pathways related to proliferation and immune response [17]. Furthermore, protein–protein interaction (PPI) network analysis has uncovered links between viral proteins (e.g., NSP7, NSP9, NSP13) and host proteins involved in centrosome processes and DNA polymerase complexes, leading to disruptions in DNA damage response and cell cycle regulation [19, 21]. Docking studies are yet another approach that have detailed interactions between the virus S protein and receptors like EGFR and VEGFR, which may influence tumor growth [20]. Additionally, proteomic analysis with tools like SAINTexpress and MSFragger has expanded our understanding of interactions between SARS-CoV-2 proteins and host proteins, revealing their roles in protein biogenesis, apoptosis resistance, immune evasion, and metabolic dysregulation [18]. These computational approaches are invaluable for uncovering the intricate web of interactions between SARS-CoV-2 and host proteins, providing critical insights into viral pathogenesis and potential therapeutic targets (Table 1).

COVID-19 in patients with malignancies

COVID-19 has emerged as a significant concern for individuals with cancer, with numerous studies indicating a notable correlation between infection of virus and mortality rates due to malignancy. For instance, reports summarising data from various regions including Europe, America and Asia have revealed higher case fatality rates among hematological malignancy (HM) patients with COVID-19 [23]. Moreover, another comparable cohort study encompassing multiple countries, including, UK, Poland, Italy, Spain, Belgium, USA, France and Turkey reported mortality rate among lymphoma patients with COVID-19 to be approximately around 30% [24]. Another retrospective study from Tertiary cancer care hospital has further underscored the occurrence rate of COVID-19 in hospitalized cancer patients to be around 6.0% higher than the general population. Notably, the case fatality rate (CFR) among cancer patients with COVID-19 has been found to be substantially higher, at 14.52%, compared to the CFR in the general population [25]. In line with this, a multicentre observational study involving 19 centres across UK, Italy, Germany and Spain highlighted about the increased vulnerability of cancer patients to COVID-19 and further showing differential mortality rates across various cancer types. In accordance with other studies, haematological malignancies have been majorly associated with poor outcomes in COVID-19 cases among cancer patients [26].

Overall, these data from various studies highlight the significant impact of COVID-19 on individuals with cancer, with heightened mortality rates observed across different cancer types. This correlation shows the complex interplay between viral infections and cancer outcomes, warranting further investigation into potential viral influences on cancer development and progression.

SARS-CoV-2 proteins regulating oncogenic pathways and *cancer* risk

SARS-CoV-2, the virus responsible for the COVID-19 pandemic, has been increasingly linked to the dysregulation of crucial oncogenic pathways, highlighting its potential role in cancer development and progression. Recently, bioinformatics studies have identified several cancer-associated molecular targets influenced by virus infection (Table 2).

SARS-CoV-2 exerts a notable influence on tumorigenesis through various mechanisms including the modulation of proliferative signaling pathways, inflammatory responses, the role of tumour suppressor molecules and oncogenes, oxidative stress and DNA damage repair pathways, epigenetic signaling, and cellular metabolism-associated pathways (Fig. 1) [19, 35–39]. One notable pathway affected by SARS-CoV-2 is the PI3K/AKT/mTOR pathway, which plays a crucial role in regulating cell proliferation and survival. The virus can also impact the MAPK pathway, another critical signaling cascade involved in cell growth and differentiation [40]. Additionally, SARS-CoV-2 has been shown

Table 1 Interaction of SARS-CoV-2 proteins with oncogenes and tumor suppressor genes modulating signaling pathways— studies

S. No	SARS-CoV-2 Proteins/ORF generating polypeptides	Type of Study and Software used	Mammalian Protein Targets (Oncogene/ Tumor Suppressor)	Signaling Pathways Altered	References
1	Spike protein (S), Non-structural protein (NSP) and Membrane protein (M)	Network analysis, Cytoscape, BiNGO	SRC, MYC, EGFR, MET, LYN, KIT, JUN, FOS, FGFR1, ERBB2, ERBB3, ERBB4, BRAF, CCND1, ABL2, ABL1 and SKI	Proliferation, migration and immune response	[17]
2	NSP7, NSP9, NSP13, NSP1, Open reading frame (ORF)3a, NSP14, NSP8, NSP5, ORF8 and NSP12	Protein–Protein Interaction (PPI) network analysis	Centrosome-associated proteins, PKA signaling components, mitotic proteins, single-stranded RNA-binding proteins, DNA polymerase alpha complex, HMOX1, SIRT5, NSD2, HDAC2, DNMT1, NEK9 and RIPK1	Cell cycle dysregulation, DNA damage response, genomic instability metabolic reprogramming, epigenetic modulation, translation and RNA processing, apoptosis and NF-κB activation	[19]
3	Spike protein	Protein–Protein Docking	EGFR, VEGFR and c-MET	EGFR, VEGFR, tumor growth, tumor invasion and c-MET signaling pathways	[20]
4	Spike protein, NSP protein and M protein	PPI network, functional enrichment and network analyses Enrichr, STRING database, Cytoscape and GEPIA 2 server	PTEN, SMAD3, SP1, CASP3, MAPK8, CDKN1B, CREB1, STAT1, PSMB8, HLA-F, HLA-A, HLA-C, IRF2 and PSMB5	cAMP-dependent, G-coupled, RTK and JAK/STAT signaling pathways	[21]
5	NSP7, NSP9, NSP13, NSP1, NSP8, ORF3a, ORF14, NSP12, protein E, ORF6, and NSP5	Proteomic analysis of virus-host PPI	CREB1, CASP3, PTEN, SMAD3, LARP1, LARP4B, PABPC1, NUP98, RAE1, DDX10, HSP90, ABCC1, MARK2, MARK3, HDAC2, NSD2, LARP1, mTOR, BRD4, BRD2, NFE2L2, KEAP1, NF-κB, eIF4E, LARP4B, HMOX1, SIRT5, NFE2L2 and DDX10	Cell cycle regulation, DNA damage repair, metabolism, epigenetic regulation, mRNA translation and NF-κB activation	[18]
6	NSP1, NSP5, NSP8, NSP13, NSP15, E, N, ORF3a, ORF6, ORF9b, ORF10 and S	Proteomic Analysis, SAINTexpress and MiST	G3BP1, G3BP2, LARP1, CK2, UPF1, MOV10, eIF4A, eIF4E, eIF4G, SRP19, SRP54, SRP72, HDAC2, TRMT1, TBK1, TBKBP1, RNF41, TOMM70, TLE1, TLE3, TLE5, NLRX1, F2RL1, NDFIP2, TRIM59, MIB1, NUP98-RAE1, ZYG11B, BRD2 and BRD4	Interferon pathway, NF-κB pathway, mTOR-regulated translational repression, stress granule formation, endoplasmic reticulum stress response, nuclear transport machinery, innate immune pathways, vesicle trafficking pathways, ubiquitination pathways, translation machinery, and protein biogenesis pathways	[22]

Various bioinformatics studies showing the interaction of SARS-CoV-2 proteins with a mammalian proteins modulating key signalling pathways. EGFR, Epidermal growth factor receptor; FGFR1, Fibroblast growth factor receptor 1; ERBB2, Receptor tyrosine protein kinase v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2; ERBB3, Receptor tyrosine-protein kinase erbB-3; ERBB4, Receptor tyrosine-protein kinase erbB-4; CCND1, Cyclin D1; ABL2, Tyrosine-protein kinase ABL2; ABL1, Abelson tyrosine-protein kinase 1; PKA, Protein kinase A; HMOX1, Heme oxygenase 1; SIRT5, Sirtuin 5; HDAC2, Histone deacetylase 2; DNMT1, DNA (cytosine-5)-methyltransferase 1; NEK9, Never in mitosis gene A-related kinase 9; RIPK1, Receptor-interacting serine/threonine-protein kinase 1; VEGFR, Vascular endothelial growth factor receptor; PTEN, Phosphatase and tensin homolog; SMAD3, Mothers against decapentaplegic homolog 3; SP1, Specificity protein 1; CASP3, Caspase 3; MAPK8, Mitogen-activated protein kinase 8; CDKN1B, Cyclin-dependent kinase inhibitor 1B; CREB1, Cyclic AMP-responsive element-binding protein 1; STAT1, Signal transducer and activator of transcription 1; PSMB8, Proteasome subunit beta type-8; HLA, Human leukocyte antigen; IRF2, Interferon regulatory factor 2; LARP1, La-related protein 1; LARP4B, La-related protein 4B; PABPC1, Polyadenylate-binding protein 1; NUP98, Nucleoporin 98; RAE1, mRNA export factor; DDX10, ATP-dependent RNA helicase DDX10; HSP90, Heat shock protein 90; ABCC1, ATP-binding cassette sub-family C member 1; MARK2, Microtubule affinity-regulating kinase 2; MARK3, Microtubule affinity-regulating kinase 3; mTOR, Mammalian target of rapamycin; BRD4, Bromodomain-containing protein 4; BRD2, Bromodomain-containing protein 2; NFE2L2, Nuclear factor erythroid 2-related factor 2; KEAP1, Kelch-like ECH-associated protein 1; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; eIF4E, Eukaryotic translation initiation factor 4E; TBK1, TANK-binding kinase 1; TBKBP1, TBK1-binding protein 1; RNF41, Ring finger protein 41; TOMM70, Translocase of outer mitochondrial membrane 70; TLE1, Transducin-like enhancer protein 1; TLE3, Transducin-like enhancer protein 3; TLE5, Transducin-like enhancer protein 5; NLRX1, NLR family member X1; F2RL1, Coagulation factor II (thrombin) receptor-like 1; NDFIP2, Nedd4 family-interacting protein 2; TRIM59, Tripartite motif-containing protein 59; MIB1, Mindbomb E3 ubiquitin protein ligase 1; NUP98-RAE1, Nucleoporin 98—RNA export factor 1; ZYG11B, Protein Zyg-11 homolog B

to interact with receptors, such as the Eph receptor, potentially disrupting downstream signaling cascades associated with oncogenesis [41]. Furthermore, dysregulation of the EGFR signaling pathway, observed in various tumour types, can be influenced by SARS-CoV-2 infection, either through overexpression or mutation within the EGFR gene [42]. Alterations in actin-binding proteins and RNA-binding proteins have also been implicated in promoting tumour growth, highlighting the additional pathways affected by the virus [21]. In the following section, we delve into the intricate correlation between SARS-CoV-2 proteins and their impact on diverse oncogenic molecules and the pathways they share.

Tumor suppressor proteins and oncogenes

Tumor initiation is the first critical step in carcinogenesis, marked by genetic and epigenetic alterations that transform normal cells into malignant ones. This process involves the inactivation of tumor suppressor genes and the activation of oncogenes, both of which disrupt normal cell regulation. The activation of oncogenic signaling pathways further drives tumor cell growth, survival and proliferation. DNA damage, often induced by environmental factors or oxidative stress, leads to mutations that contribute to genomic instability [43]. Such damages are further induced by oxidative stress that generates reactive oxygen species (ROS). In addition to the genetic alterations, epigenetic modifications, such as DNA methylation and histone changes, also alter gene expression, often silencing tumor suppressors or activating oncogenes [44]. Following tumor initiation, the metabolic reprogramming of cells is rewired to meet the energy demands of rapidly dividing cells, thereby fostering tumorigenesis [45]. Collectively, these factors create an environment conducive to the emergence and expansion of initiated cells, setting the stage for tumor promotion. Notably, SARS-CoV-2 proteins have been implicated in regulating the key regulators of these hallmarks, that contribute to cancer initiation and promotion (Fig. 2) [19].

In normal cellular physiology, proto-oncogenes and tumor suppressor genes tightly regulate cellular growth, differentiation and essential biological processes. Dysregulation of these genes, either through the loss of tumor suppressor function or the gain of oncogene function, is a hallmark of cancer development [46]. In this context, SARS-CoV-2 and its proteins exert a significant influence on the regulation of such genes. For instance, pRB and p53, the two major tumor suppressor genes which play central roles in the regulation of proliferation and survival of the cells are targeted by SARS-CoV-2 non-structural proteins, NSP 15 and NSP 3, respectively [35, 36, 47]. NSP-15, an endonuclease, via its retinoblastoma protein-binding motif (LXCXE/D) binds to hypo-phosphorylated form of pRB, and induces its nuclear export into the cytoplasm where pRB associates with ubiquitin leading to its proteasomal degradation [35]. On the other hand, p53 is degraded via the interaction of the SARS unique domain (SUD) and papain-like protease of SARS-CoV-2 NSP-3 protein with E3 ubiquitin ligase ring-finger and CHY zinc-finger domain-containing 1 (RCHY1) [36]. Loss of function of both of these genes leads to cell cycle dysregulation ultimately leading to uncontrolled proliferation and survival resulting in cancer development [48].

An oncogene targeted by SARS-CoV-2 is TUBA1C, which is significantly upregulated in tumor tissues. TUBA1C plays a role in promoting proliferation and oncogenesis, particularly in glioma and pancreatic ductal adenocarcinoma, by regulating the cell cycle progression [49, 50]. Interestingly, mass spectrometry analysis of HCT116 cells transfected with the nucleocapsid protein of SARS-CoV-2 has shown a notable increase in the expression of TUBA1C gene [51]. SARS-CoV-2 impact on increased TUBA1C expression pattern suggests a potential role for the virus in promoting proliferative signaling, an important hallmark of cancer.

Moreover, mucin, characterized as an oncogene emerges as another crucial link between SARS-CoV-2 and cancer. Many studies have consistently demonstrated the oncogenic role of mucin genes including MUC-1, MUC-5AC, MUC-16, MUC-4 and TAG-72 with their overexpression often associated with poor prognosis of cancer [52–54]. Further, an elevated mucin-1 can activate TGF-α and EGFR-induced Receptor Tyrosine Kinase (RTK) signaling, leading to increased cell proliferation and survival [55]. Remarkably, a clinical study has revealed that critically ill COVID-19 patients also display elevated level of MUC-5AC, MUC-1 and TAG-72 [56, 57]. This notable elevation of mucins in COVID-19 patients not only reflects a significant aspect of COVID-19 pathology but also poses a potential risk factor for cancer progression in affected individuals. However, further extensive investigation is required to unravel the underlying mechanisms.

Oncogenic signaling pathways

Dysregulation in key signaling pathways including RAS/RAF/MEK/ERK/PI3K/AKT signaling that play crucial role in cell growth, survival and proliferation generally leads to cancer development and progression [58]. Moreover, the SARS-CoV-2 emerges as a significant player in regulating oncogenic signaling pathways associated with cell proliferation and growth. Specifically, it impacts pathways like PI3K/AKT/mTOR and MAPK [59]. One of its target receptors is the erythropoietin-producing hepatocellular carcinoma (Eph) receptor,

Table 2 In silico studies for SARS-CoV-2 or its proteins interaction with various molecular targets linked to oncogenesis

S.No	GEO Accession	Software Used	Perturbed Biological functions	Molecular Targets, TFs, and miRNAs	Oncogenesis Implication	References
1	**GSE157103** **GSE75097**	LASSO, Random Forest, Support Vector Machine, Enrichr, STRING, Cytoscape, CytoHubba, MCODE, NetworkAnalyst, DSigDB, CIBERSORT	DNA repair, cell cycle regulation, bladder cancer, Kaposi sarcoma-associated herpesvirus infection, and metabolic pathways	TP53, CCND1, MDM2, RB1, HIF-1A, EP300, STAT3, CDK2, HSP90AA1, and PPARG	The study reveals key molecular pathways and genes, such as TP53, HIF-1A, and STAT3, that are implicated in COVID-19 suggesting a potential link to oncogenesis	[27]
2	**GSE178331** **GSE150392** **GSE66360** **GSE150392** **GSE162736** **GSE178246**	R, p-adjust function, DESeq2, GEO2R, clusterProfiler, STRING, Cytoscape, GeneMANIA, TRRUST, NetworkAnalyst, ggplot2	TNF signaling pathway, IL-17 signaling pathway	IL-1B, CXCL8, CTNNB1, FOS, PTGS2, EGR2, NFKBIA, ZFP36 miR-26b-5p, miR-335-5p, miR-124-3p, let-7b-5p, let-7a-5p, and miR-146a-5p	COVID-19-induced inflammation may exacerbate AMI, influencing cancer-related pathways	[28]
3	**BioGRID, STRING, SARS2-Human Proteome Interaction Database SHPID**	Cytoscape, CentiScaPe	Cytokine signaling, cell cycle regulation, and apoptosis	RPL11, MDM2, TP53, RPS27A, ACTB, FN1, COL2A1, ITGA5, ALDOA, RRM2B, BAG2, and HGS	RPS27A- Involved in cancer progression through regulation of p53 and MDM2 interaction, influencing cellular stress response TP53- Functions as a tumor suppressor by inducing cell cycle arrest and apoptosis, counteracted by MDM2 HIF1alpha- Responds to oxidative stress and is upregulated in cancer and COVID-19 conditions	[29]
4	**GSE152418** **GSE119336**	R LIMMA package, jvenn, Enrichr, STRING, Cytoscape, CytoHubba, NetworkAnalyst	Glyoxylate and dicarboxylate metabolism, fatty acid biosynthesis, metabolism of steroids, bile acid and bile salt metabolism	SCD, ACSL5, ACAT2, HSD17B4, ALDOA, ACSS1, ACADSB, CYP51A1, PSAT1, and HKDC1	COVID-19 may exacerbate ICC through shared metabolic and immune disruptions, highlighting new therapeutic targets and drug opportunities	[30]
5	**GSE196822** **GSE119794**	DEseq2 R, Enrichr, STRING, Cytoscape, CytoHubba, JASPAR, MiRTarBase, NetworkAnalyst	Central carbon metabolism in cancer, Neutrophil extracellular trap formation, Viral carcino- genesis, and Transcriptional misregulation in cancer	ESPL1, HJURP, MKI67, KIF4A, CDK1, TOP2A, CCNB2, UBE2C, AURKB, TPX2 FOXC1, GATA2, YY1, FOXL1, hsa-miR-16-5p, and has-miR-193b-3p	Shared DEGs between COVID-19 and pancreatic cancer are involved in pathways related to viral genome replication, cancer development, immune system regulation, and cell cycle progression, suggesting a potential link between viral infections and cancer progression	[31]

Table 2 (continued)

S.No	GEO Accession	Software Used	Perturbed Biological functions	Molecular Targets, TFs, and miRNAs	Oncogenesis Implication	References
6	**GSE147507** **GSE150316**	DESeq2, StringTie, STAR, samtools, FastQC, MultiQC, REVIGO, EBSeq, Moomin, IsoformSwitchAnalyzeR, TEtools, TFBSTools, MAFFT, meta-CATS, GREAT, DAVID	PI3K/AKT signaling pathway, Neutrophil and granulocyte activation, IL-1-mediated signaling pathway, Proteolysis, Stress-activated signaling cascades, Amoebiasis pathways, p75NTR-mediated signaling pathways, TrkA receptor signaling pathways, and IFN-α/β signaling pathway	PIK3CA, PIK3CB, PIK3CD, PIK3CG, AKT1, AKT2, AKT3, PTEN, MTOR, CXCL8, IL-1B, IL-6, IL-8, IL-10, IL-17A, IL-18, TNF, NF-κB, IL1R1, IL1R2, IL1RN, MYD88, IRAK4, IRAK1, TRAF6, CTSB, CTSD, CTSL, CTSZ, MMP2, MMP9 MMP14, UCHL1, UCHL3, MAPK1, MAPK3, MAPK8, MAPK9, JNK1, JNK2, JUN, ATF2, ATF4, ACTB, ACTG1, GTPBP2, RHOA, RHOB, RHOC, RAC1, ARPC1B, NTRK1, NTRK2, NTRK3, P75NTR, GRB2, SHC1, SOS1, TRKB, TRKC, PLCG1, IFNA1, IFNA2, IFNA4, IFNB1, IFNAR1, IFNAR2, JAK1, JAK2, STAT1, STAT2, CLTC, DNM2, AP2M1, PIK3R1, PIK3R2, TP53, MYC, KRAS, BRAF, EGFR, CDK4, CDK6, CCND1, RB1, CDK1, CDK2, CCNA2, CCNB1, CCNE1, and E2F1	This study highlights key genes and pathways central to oncogenesis, including PI3K/AKT signaling which drives uncontrolled cell proliferation and survival. Dysregulation of NF-κB signaling and inflammation-related cytokines IL6, and TNF further promote cancer progression by creating a tumor-supportive microenvironment. Additionally, mutations in tumor suppressors like TP53 and oncogenes such as KRAS contribute to cancer development and resistance to treatment	[32]
7	**13 TCGA cancer cohorts**	Single-Sample Gene-Set Enrichment Analysis ssGSEA, Gene-Set Enrichment Analysis GSEA, Weighted Gene Co-Expression Network Analysis WGCNA	Cell cycle, mismatch repair, TGF-β, Wnt signaling, VEGF, Notch signaling, T cell receptor signaling, and Jak-STAT signaling	ACE2, PD-L1, EOMES, IRF4, and TBX21	ACE2 upregulation correlates with reduced cancer progression, decreased cell proliferation, stemness, and EMT, as well as downregulation of oncogenic pathways, suggesting ACE2 may act as a protective factor against cancer progression	[33]
8	**GSE111016** **GSE171110**	R, Enrichr, STRING, Cytoscape, Cytohubba, GeneMANIA, NetworkAnalyst, DisGeNET	Th1 and Th2 cell differentiation, chemical carcinogenesis- receptor activation, hematopoietic cell lineage, Nucleotide metabolism, and renin-angiotensin system	ACE, ALDH1L, CYP1A1, PYGL, KLF5, NNMT, PHGDH, IDO1, EME1, CD52, MYBL2, CDC25A, BCL6, CD3D, and ESM1	The study suggests that key genes such as ACE, KLF5, IDO1, and CDC25A, which are implicated in the pathological mechanisms of both COVID-19 and sarcopenia, may also contribute to oncogenesis through pathways such as chemical carcinogenesis – receptor activation, cellular senescence, and alterations in the tryptophan metabolic pathways	[34]

Listed here are various bioinformatics studies that highlight SARS-CoV-2's interactions with mammalian target genes, the biological pathways altered, and their implications for oncogenesis. CCND1, Cyclin D1; MDM2, Mouse Double Minute 2 Homolog; EP300, E1A Binding Protein p300; CDK2, Cyclin-Dependent Kinase 2; HSP90AA1, Heat Shock Protein 90 Alpha Family Class A Member 1; PPARG, Peroxisome Proliferator-Activated Receptor Gamma; IL1B, Interleukin 1 Beta; CXCL8, C-X-C Motif Chemokine Ligand 8; CTNNB1, Catenin Beta 1; PTGS2, Prostaglandin-Endoperoxide Synthase 2; EGR2, Early Growth Response 2; NFKBIA, Nuclear Factor Kappa B Inhibitor Alpha; ZFP36, Zinc Finger Protein 36; ACTB, Actin Beta; FN1, Fibronectin 1; COL2A1, Collagen Type II Alpha 1 Chain; ITGA5, Integrin Alpha V; ALDOA, Aldolase A; RRM2B, Ribonucleotide Reductase Regulatory Subunit M2B; SCD, Stearoyl-CoA Desaturase; ACSL5, Acyl-CoA Synthetase Long-Chain Family Member 5; ACAT2, Acetyl-CoA Acetyltransferase 2; HSD17B4, Hydroxysteroid 17-Beta Dehydrogenase 4; ACSS1, Acetyl-CoA Synthetase 1; ACADSB, Acyl-CoA Dehydrogenase Short-Chain; PSAT1, Phosphoserine Aminotransferase 1; HKDC1, Hexokinase Domain Containing 1; HJURP, Holliday Junction Recognition Protein; KIF4A, Kinesin Family Member 4A; TOP2A, Topoisomerase II Alpha; CCNB2, Cyclin B2; UBE2C, Ubiquitin Conjugating Enzyme E2 C; AURKB, Aurora Kinase B; TPX2, Targeting Protein for Xenopus Kinesin-Like Protein 2; FOXC1, Forkhead Box C1; GATA2, GATA Binding Protein 2; PIK3CA, Phosphoinositide-3-Kinase Catalytic Alpha Subunit; AKT1, AKT Serine/Threonine Kinase 1; AKT2, AKT Serine/Threonine Kinase 2; AKT3, AKT Serine/Threonine Kinase 3; IL6, Interleukin 6; IL1R1, Interleukin 1 Receptor Type 1; MYD88, Myeloid Differentiation Primary Response 88; IRAK4, Interleukin-1 Receptor-Associated Kinase 4; TRAF6, TNF Receptor-Associated Factor 6; UCHL1, Ubiquitin C-Terminal Hydrolase L1; ACTG1, Actin Gamma 1; GTPBP2, GTP Binding Protein 2; RHOA, Ras Homolog Family Member A; RAC1, Ras-Related C3 Botulinum Toxin Substrate 1; ARPC1B, Actin-Related Protein 2/3 Complex Subunit 1B; NTRK1, Neurotrophic Receptor Tyrosine Kinase 1; P75NTR, P75 Neurotrophin Receptor; GRB2, Growth Factor Receptor-Bound Protein 2; SHC1, SHC Adapter Protein 1; SOS1, Son of Sevenless 1; TRKB, Tropomyosin Receptor Kinase B

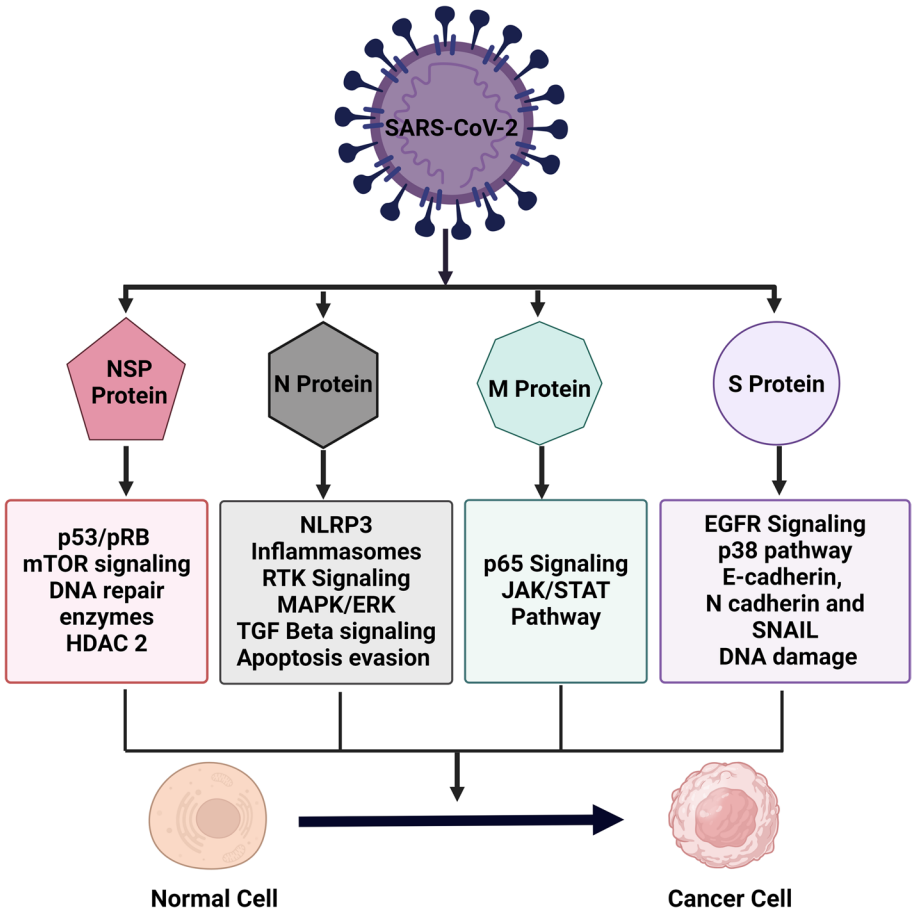


Fig. 1 Schematic diagram illustrating various key oncogenic signaling molecules or pathways targeted by SARS-CoV-2 NSP, N, M and S protein. The activation of oncogenic pathways can lead to the conversion of a normal cell into a cancer cell. This image was created using BioRender software

which belongs to the family of receptor tyrosine kinases (RTKs) and found in various tissues and organs, including the lung, liver, colon, small intestine, heart, prostate and kidney. Eph receptors also serve as a potential entry point for the SARS-CoV-2 virus, potentially disrupting downstream signaling cascades. Based on existing literature, a study suggested that the spike protein of the virus can stimulate Eph receptors, leading to the activation of pathways such as PI3K/AKT/ERK [41]. Any perturbation within these pathways, whether caused by the activation or overexpression of extracellular signaling molecules or mutations in RTKs, has the potential to strongly drive oncogenesis [59]. Hence, the influence of SARS-CoV-2 on oncogenic signaling pathways, especially through its interaction with Eph receptors, underscores its potential role in promoting cancer-related processes.

What makes this connection more fascinating is the involvement of epidermal growth factor receptor (EGFR) signaling pathway. Dysregulation of EGFR signaling is observed in various tumor types with either overexpression or mutation within the EGFR gene known to fuel the oncogenic process [60]. Intriguingly, recent research investigations have suggested that EGFR might serve as one of the potential receptors with which SARS-CoV-2 spike RBD domain interacts [42]. Docking analysis has further shown comparable binding affinity between the viral spike protein and EGFR/VEGFR in glioma cells, similar to angiotensin converting enzyme 2 (ACE2) [20]. Given that EGFR and VEGFR are commonly expressed in many tumor types, including glioma cells [20, 61], this interaction suggests that the virus could activate EGFR and its downstream signaling, potentially exacerbating oncogenic pathways. Interestingly, various bioinformatic and in vitro studies have confirmed increased EGFR signaling and its downstream pathways, such as AKT and ERK1/2, in SARS-CoV-2 infected cells mediated by the spike RBD domain [42, 62–64]. Therefore, these findings underscore the oncogenic implications of SARS-CoV-2, specifically its involvement in key cellular signaling pathways, notably implicating EGFR.

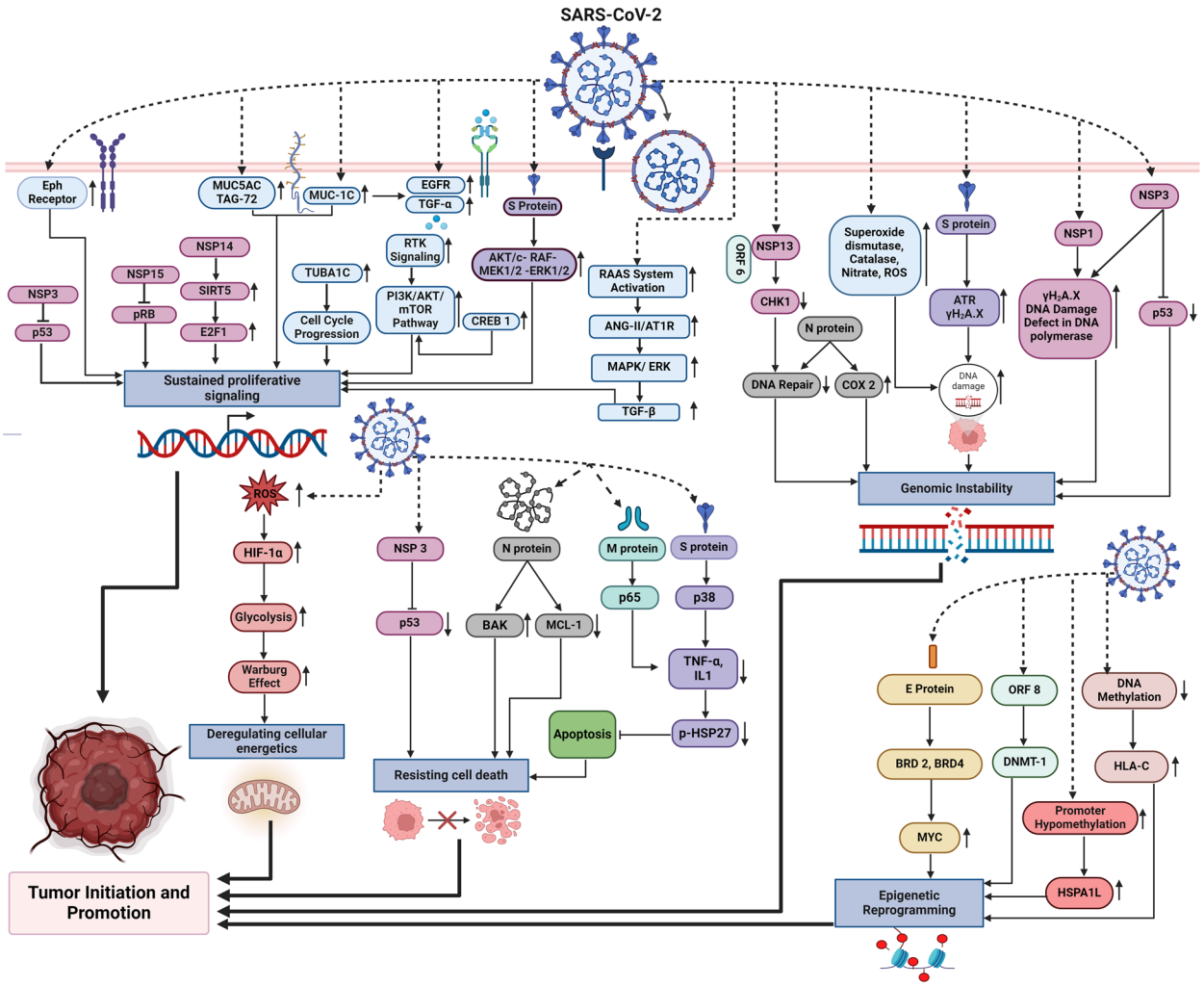


Fig. 2 Schematic illustration depicting the shared mechanisms between SARS-CoV-2 and key hallmarks of cancer including sustained proliferative signaling, resisting cell death, genomic instability, dysregulated cellular metabolism and epigenetic reprogramming. The diagram highlights how SARS-CoV-2 interacts with critical oncogenic signaling molecules or pathways. Specific SARS-CoV-2 proteins involved in these processes are marked: NSP (Non-Structural Proteins), N (Nucleocapsid Protein), M (Membrane Protein) and S (Spike Protein). p53, Tumor Protein 53; pRB, Retinoblastoma Protein; RAAS, Renin–Angiotensin–Aldosterone System; E2F1, E2F Transcription Factor 1; SIRT5, Sirtuin 5; ANGII/AT1R, Angiotensin II/Angiotensin II Type 1 Receptor; MAPK/ERK1/2, Mitogen-Activated Protein Kinase/Extracellular Signal-Regulated Kinase 1/2; TGF-β, Transforming Growth Factor Beta; MUC1C, Mucin 1, Cell Surface Associated; MUC5AC, Mucin 5AC; TUB1AC, Tubulin Alpha; CREB, cAMP Response Element-Binding Protein; Eph receptor, Ephrin Receptor; RTK, Receptor Tyrosine Kinase; TGFR, Transforming Growth Factor Receptor; ATR, Ataxia Telangiectasia and Rad3-Related Protein; C-RAF, RAF Proto-Oncogene Serine/Threonine-Protein Kinase; HSP27, Heat Shock Protein 27; BAK, BCL2 Antagonist/Killer; MCL1, Myeloid Cell Leukemia 1; HLAC, Human Leukocyte Antigen C; HSPAIL, Heat Shock Protein A1-like; DNMT1, DNA Methyltransferase 1; ROS, Reactive Oxygen Species; NO, Nitric Oxide; HIF1-α, Hypoxia-Inducible Factor 1-Alpha. This image was created using BioRender software

Oxidative stress, DNA damage and apoptosis

The interplay between oxidative stress, DNA damage and apoptosis emphasizes the critical role of DNA damage response (DDR) pathways in maintaining genomic integrity and preventing cancer initiation and progression. For instance, in a normal cell, the DDR pathway plays a crucial role in preserving genomic integrity through cell cycle control, DNA repair and apoptosis. However, in cancer cells, dysregulation of DNA replication, repair pathways and cell cycle checkpoints, and increased oxidative stress contribute to genomic instability and resistance to apoptosis thereby increasing cancer susceptibility [65, 66]. Notably, emerging evidence suggests that SARS-CoV-2 proteins have critical role in dysregulating DDR pathways and resisting cell death similar to cancer cells [19]. Understanding the interplay between viral infection and genomic instability may shed light on potential mechanisms

underlying COVID-19 pathogenesis and its association with cancer risk.

For example, the NSP13 protein of SARS-CoV-2 is a promising target for antiviral drugs due to its high sequence conservation and crucial function in the replication of virus [67]. Cell cycle arrest, γH2AX histone phosphorylation, replication fork stress, and DNA damage are caused by the interaction of NSP13 protein with DNA polymerase δ [37]. The stress or any defects in replication fork is known to contribute to tumor development [68]. Given the high similarity (99.8%) between NSP13 of SARS-CoV and SARS-CoV-2 [69], it is reasonable to infer that both may employ the similar mechanism to target DNA replication. Moreover, SARS-CoV-2 infection impairs DNA repair pathways, mediated by N and RNA-binding proteins, ORF-6 and NSP13, which degrade DNA damage checkpoint protein CHK1 [70]. Additionally, SARS-CoV-2 infection also induces overexpression of DNA damage-related checkpoints, such as ATR, pCHK1 and γH2AX expression [71]. These findings strengthened the ability of the virus to induce genomic instability, potentially contributing to tumor development.

SARS-CoV-2 employs multiple mechanisms to interfere with cellular processes, potentially promoting cancer development. The nucleocapsid (N) protein activates Cyclooxygenase-2 (COX-2) via NF-κB and C/EBP sites, potentially leading to increased COX-2 expression [72]. Elevated COX-2 levels are linked to cancer progression through genomic instability and DNA damage [73–75]. Since SARS-CoV-2 N protein shares 90% similarity with SARS-CoV, suggesting a similar potential for COX-2 dysregulation and genomic instability [76]. SARS-CoV-2 infection also upregulates C-reactive protein and prooxidant genes, further inducing DNA damage [77–81]. The increased ROS species production is another method of causing genomic instability. In a tadpole model, it has been demonstrated that peptides generated from the virus's spike protein increase the levels of nitrites, hydrogen peroxide, and reactive oxygen species (ROS) and enhance the activities of catalase and superoxide dismutase [82]. Increased expression of oxidative markers is known to lead to ROS production, which plays a role in various stages of tumorigenesis [83]. Therefore, it is plausible that the Spike protein, through its impact on oxidative markers and ROS expression, may contribute to DNA damage and oncogenesis.

Previous studies suggest that SARS-CoV-2 infection, particularly its M and spike proteins, activates p38 kinase and inflammatory pathways, leading to cytokine storm [84–87]. This cascade is known to result in the phosphorylation of heat shock protein 27 (HSP-27), and interestingly a study has explored this relation and demonstrated the upregulation of p38 kinase and the subsequent phosphorylation of its downstream target HSP-27, following SARS-CoV-2 infection [88, 89]. The phosphorylation of HSP-27 is known to impede apoptosis-related processes and associated with poor prognosis in cancers [67, 90]. The activation of HSP-27 by viral proteins may contribute to cancer development by disrupting critical cell death mechanisms.

Another protein responsible for evading apoptosis is SARS-CoV-2 NSP-3 protein. The SARS unique domain (SUD) and papain-like protease of NSP3 interacts with RCHY1, leading to the degradation of the tumor suppressor protein p53 [36]. Since p53 is crucial for apoptosis and cancer prevention [91, 92], its downregulation by SARS-CoV-2 NSP-3 may promote tumorigenesis by inhibiting cell death pathways. Additionally, NSP-14 of SARS-CoV-2 interacts with SIRT-5, enhancing its activity [93]. SIRT-5 is implicated in inhibiting apoptosis and promoting hepatocellular carcinoma progression [94], the interaction facilitated by NSP-14 could contribute to cell death evasion, potentially fostering tumor development.

Recent studies reveal that SARS-CoV-2 N protein interacts with the anti-apoptotic protein MCL1, enhancing viral replication by stabilizing MCL1 through the recruitment of USP15. This prevents MCL1 ubiquitination and allows it to inhibit mitochondrial-mediated apoptosis by sequestering BAK [95]. As MCL1 overexpression is linked to various cancers, its stabilization by SARS-CoV-2 N protein represents another mechanism promoting cell death evasion and potentially contributing to the cancer phenotype [96, 97]. These findings highlight the intricate interactions between viral proteins and apoptotic pathways, suggesting potential therapeutic targets for both viral infections and cancer. Further research is needed to fully understand these interactions and develop strategies to mitigate the oncogenic effects of SARS-CoV-2.

Dysregulation of cellular metabolism and epigenetic alterations

Epigenetics, the study of heritable changes in gene expression not stemming from DNA sequence alterations, plays a critical role in normal embryonic development. However, dysregulation of epigenetic mechanisms like DNA methylation and histone modifications contributes to oncogenesis [98, 99]. Concurrently, cancer cells also exhibit metabolic alterations, including shifts in glycolysis, glutamine metabolism and mitochondrial function, supporting increased proliferation further resulting in cancer initiation and growth [100–102]. Similarly, the SARS-CoV-2 also possess the ability to induce epigenetic changes and deregulate cellular metabolism to promote their replication, potentially exacerbating cancer

development. This intricate interplay between viral infection, epigenetics and metabolic dysregulation underscores the multifaceted nature of oncogenesis.

SARS-CoV-2 proteins, particularly ORF-8, interact with DNMT-1 and BRD4, potentially disturbing critical epigenetic modifiers implicated in cancer progression [19, 38, 103]. Moreover, in addition to CpG methylation SARS-CoV-2 infection induced epigenetic changes, like hypomethylation of the HSPA1L promoter, that may also contribute to cancer development [104, 105]. Dysregulation of HLA-C expression via epigenetic mechanisms that is also responsible for the development of various cancers including lung or prostate cancer further emphasize the potential cancer risk associated with COVID-19 [106, 107].

Additionally, SARS-CoV-2 has potential role in dysregulating cellular metabolism for instance the interaction of NSP14 with SIRT-5 could enhance SIRT-5 activity, potentially remodelling serine catabolism [40]. Previous studies have highlighted the significance of increased SIRT-5 activity in tumor development and its role in the dysregulation of serine catabolism, a key factor driving cellular proliferation in tumors [108], Hence, it is noteworthy that NSP14 by enhancing SIRT-5 activity might remodel the serine catabolism and facilitate tumor spread. These findings emphasize the complex interplay between SARS-CoV-2, epigenetics and deregulated metabolism, highlighting potential mechanisms underlying increased cancer risk associated with COVID-19.

Tumor-associated Inflammation

Inflammation within the tumor microenvironment (TME) plays a pivotal role in cancer progression, with cytokines orchestrating cell-to-cell interactions that foster tumor growth and survival [109]. Chronic inflammation plays a crucial role in tumor development by shaping the TME and promoting tumor progression. It also shifts the balance toward tumor advancement by enhancing immune escape mechanisms. Notably, SARS-CoV-2 exacerbates this process by targeting key regulators of inflammation and immune evasion. In this section and the following one, we will explore in detail how these viral proteins contribute to these two critical hallmarks of cancer (Fig. 3) [109, 110]. Notably, SARS-CoV-2-induced cytokine storms exacerbate this inflammatory milieu, potentially accelerating cancer development. Cytokines like interleukin-6 (IL-6), interleukin-1 (IL-1) and tumor necrosis factor α (TNFα), upregulated during severe COVID-19 infection, are known mediators of pro-tumorigenic signaling, fostering oncogenesis and metastatic progression [111].

The S1 subunit of the SARS-CoV-2 spike protein induces the production of IL-1β, IL-6, and IL-8 in various cell types, including lung and intestinal epithelial cells. Lung cells exhibit a cell type-specific response with activation of ERK1/2-MAPK and NF-κB pathways, leading to IL-1β production, while intestinal cells increase IL-6 and IL-8 production independent of these pathways [112]. This tissue-specific response suggests variability in the cancer risk associated with SARS-CoV-2 infection. Activation of these pathways and secretion of inflammatory cytokines are strongly linked to cancer risk [113–115]. Additionally, another study also provided evidence supporting the role of spike protein in activating NF-κB and MAPK pathways as well as cytokine production in A549 lung cancer cells [85]. Moreover, spike protein persistence in the blood post-acute COVID-19 raises concerns about long-term complications, as continual presence can perpetuate chronic inflammation, a key driver of tumor growth [116, 117]. The SARS-CoV-2 spike protein activates the MEK/ERK pathway in lung vascular smooth muscle and endothelial cells, along with upregulating p38 kinase, leading to the production of inflammatory cytokines, such as IL6, CXCL8, CXCL10 and TNF-α [86, 118]. Additionally, Toll-like receptors (TLR) detect the spike protein, which activates the NF-κB pathway and causes innate immune and epithelial cells to produce inflammatory mediators [87].

Markedly, an interesting research has revealed that in the case of triple-negative breast cancer cells with increased ACE2 expression, the M protein induces aggressive characteristics like proliferation, stemness and metastasis by activating the NF-κB pathway and upregulating epithelial mesenchymal transition (EMT)-associated genes and inflammatory cytokines. Co-culture with M protein-treated cells induces ACE2 expression and transforms non-aggressive cells towards an aggressive phenotype, mediated by the crosstalk of NF-κB and Jak/STAT3 pathways, IL-6, IL-8 and TNFα expression, and upregulation of EMT genes [84].

The findings underscore the interconnected relationship between SARS-CoV-2 proteins, inflammation and cancer. The ability of viral proteins to induce cytokine storms and activate key signaling pathways associated with cell survival, proliferation and inflammation suggests a potential link between COVID-19 infection and cancer development. However, further research is needed to fully understand the underlying mechanisms and implications for cancer risk.

Immune escape

Immune evasion is vital for cancer cell proliferation and metastasis [119]. Similarly, SARS-CoV-2 also employs strategies to evade the host immune response, similar to mechanisms observed in cancer cells [120]. This immune evasion in COVID-19 patients leads to prolonged viral

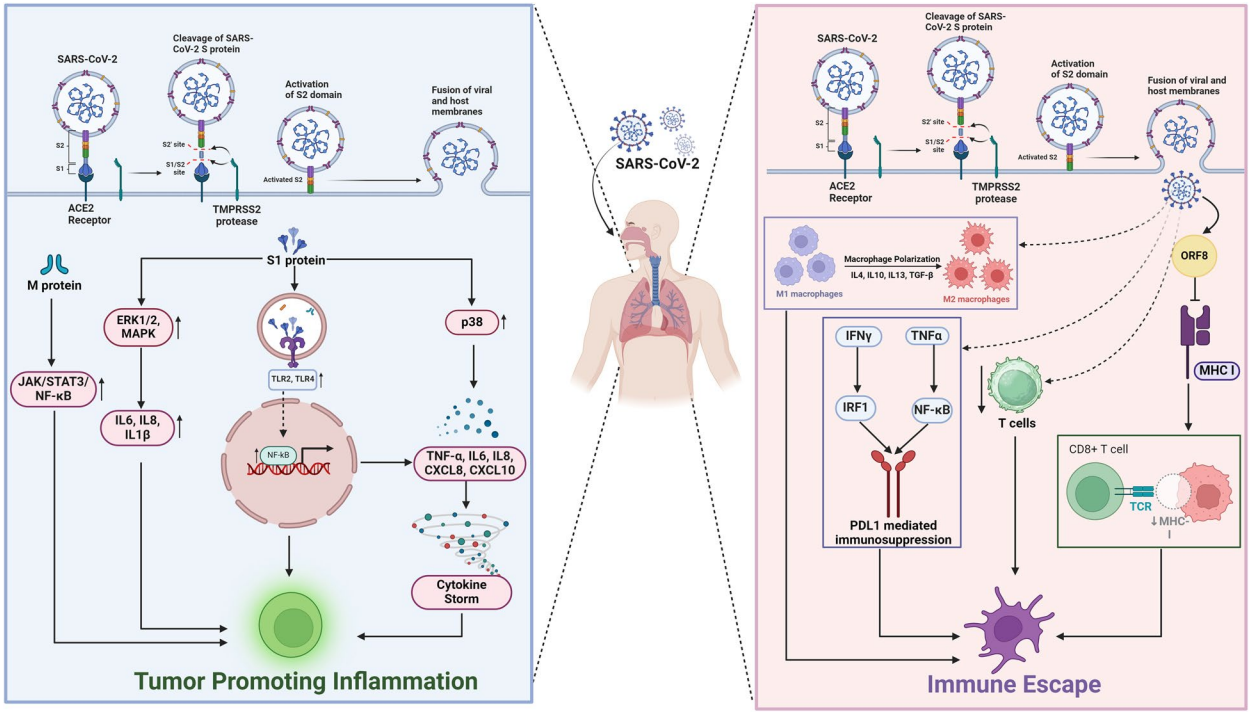


Fig. 3 The impact of SARS-CoV-2 on tumor-related inflammatory markers and mechanisms of immune evasion is depicted in the figure, illustrating how viral proteins interact with critical molecular targets within inflammatory and immune pathways. TNF-α, Tumor Necrosis Factor-Alpha; IL1, Interleukin 1; PDL1, Programmed Death-Ligand 1; COX 2, Cyclooxygenase 2; ORF 8, Open Reading Frame 8; p38, p38 Mitogen-Activated Protein Kinase; IL1-β, Interleukin 1 Beta; JAK/STAT, Janus Kinase/Signal Transducer and Activator of Transcription; CHK1, Checkpoint Kinase 1; NFκB, Nuclear Factor Kappa B. This image was created using BioRender software

presence, which can further contribute to cancer development through various mechanisms [121].

The cytokine storm and immune dysregulation are two important factors. As per the recent clinical studies the immune system produces an increased amount of pro-inflammatory cytokines, such as IL-6, IL-1β, and TNF-α, in severe COVID-19 cases. This excessive release can damage tissues and organs, overwhelming the immune system and impairing its ability to target the virus effectively [70]. As a result, the dysregulated immune response leads to impaired adaptive immunity, where cytotoxic T cells and B cells fail to function optimally, allowing the virus to persist [122]. Additionally, SARS-CoV-2 can also stimulate the activation of immunosuppressive cells, such as myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), which suppress the activity of cytotoxic T cells and NK cells, further aiding in viral persistence. The virus can induce the release of immunosuppressive cytokines like IL-10 and TGF-β, which inhibit effective immune responses and promote tumorigenic microenvironment. This leads to the prolonged presence of the virus in the body, inducing chronic inflammation, creating a microenvironment conducive to viral persistence, and promoting oncogenesis [123].

Moreover, Toll-like receptor (TLR) activation by the virus, a part of the innate immune system, can lead to prolonged viral persistence. While TLR activation is intended to initiate immune responses, excessive activation can lead to chronic inflammation and immune suppression, aiding in viral persistence and immune evasion [124]. Another interesting finding by Huot et al. identified persistent SARS-CoV-2 infection in macaques, with viral RNA and antigens detectable in lung macrophages (BALF Mac) up to 221 days post-infection. This persistence was associated with the decreased production of IFN-γ in NK cells and BALF Mac, which weakened the immune response. Remarkably, it was demonstrated that the peptide V3-11, which is generated from the SARS-CoV-2 spike protein, binds to MHC-E, hence impeding NK cell function and facilitating viral immune evasion. These findings reveal how SARS-CoV-2 can persist in the body and evade immune detection, with implications for long-term health outcomes and treatment strategies [125]. Notably, SARS-CoV-2 utilizes ORF-8 protein to decrease MHC class I molecule expression, making infected cells less detectable to immune cells [126]. In a similar way, various tumor types including breast cancer, melanoma, colorectal cancer and cervical cancer employ

this strategy to downregulate MHC class I expression, evading T cell cytotoxicity [127–130].

Secondly, the polarization of M2 macrophages, known for promoting immunosuppression in the tumor microenvironment, is also observed in COVID-19. SARS-CoV-2 triggers M2-like responses via Toll-like receptor 2 (TLR2) activation in macrophages, initiating a hyperinflammatory state involving neutrophils and $CD4^+$T cells [131]. This interplay fosters a feedback loop between macrophages and neutrophils, characterized by the secretion of cytokines, such as TGF-β and IL-1β [132–134]. The secretion of TGF-β driven by the interaction of macrophages and neutrophils has the tendency to polarize macrophages towards an M2 state [132–134]. Ultimately, this immune cell activation, including M2-like responses, cultivates an immunosuppressive milieu facilitating the tumor growth and likely contributing to cancer progression in COVID-19 [135].

T cell depletion is an another shared feature between SARS-CoV-2 and cancer. In non-severe COVID-19 cases, decreased T and B cells are observed, similar to the reduction in tumor-infiltrating lymphocytes, including cytotoxic T cells as observed in cancer cells that helps them avoid immune surveillance [136, 137]. Moreover, SARS-CoV-2 also induces upregulation of PD-L1 in lung tissues, possibly through interference with IFN-IRF1 and NF-κB axes, promoting immune suppression [138]. In a similar fashion, elevated PD-L1 levels in cancer inhibit T cell responses thereby promoting immune evasion [138]. Overall, these shared pathways illustrate the adeptness of the virus in modulating the immune response similar to that seen in cancer cells.

EMT, stemness and hypoxia

In cancer development, angiogenesis and metastasis are pivotal processes influenced by hypoxia and EMT [66, 139, 140]. Hypoxia, typical in solid tumors, activates pathways like HIF-1α, promoting both angiogenesis and EMT, where epithelial cells acquire mesenchymal traits leading to spread of tumor to distant part of the body [141]. Recent studies hint at SARS-CoV-2 proteins potentially exacerbating these processes, disrupting cellular signaling pathways associated with EMT and tumor angiogenesis, further escalating cancer risks (Fig. 4).

The Renin–Angiotensin–Aldosterone System (RAAS) exhibits dysregulation in both cancer and SARS-CoV-2 infection, establishing a significant connection between these two conditions [139]. It disrupts the balance of key components, particularly ACE2. This disruption favors the Angiotensin-Type 2 (AT II)-AT1R axis, leading to increased AT II activity and downregulation of ACE2 [142, 143]. Elevated AT II levels not only promote angiogenesis through increased angiopoietin-2 protein but also activate cancer-associated fibroblasts (CAFs). These CAFs are significant contributors to cancer progression, as they stimulate angiogenesis, modulate the extracellular matrix and release growth factors [144]. Activation of CAFs is also associated with increased collagen-1 production which leads to fibrosis. Fibrosis, in turn, reduces blood flow and induces hypoxia which in turn promotes angiogenesis by upregulating HIF-1 alpha [145]. Additionally, the elevated AT II levels induced by SARS-CoV-2 infection have been implicated in promoting the development of cancer stem cells, which are associated with cancer initiation, metastasis and relapse [146]. Moreover, AT II has been shown to enhance cell migration and matrix metalloproteinase expression, indicating its potential role in facilitating metastasis through various signaling pathways [147]. Thus, the dysregulation of RAAS during SARS-CoV-2 infection not only promotes angiogenesis but also enhances the metastatic potential of cancer cells, highlighting the intricate relationship between viral infection and cancer progression. In various studies, the AT II – AT I receptor axis has been found to elevate vascular endothelial growth factor (VEGF) expression, promoting angiogenesis in solid tumors such as ovarian, breast and bladder cancers [148, 149]. This increased VEGF production supports tumor growth by facilitating the formation of new blood vessels and exacerbating hypoxia in the TME [150, 151].

Additionally, the SphK/S1P/S1PR pathway, known as the sphingolipid rheostat signaling, is activated during SARS-CoV-2 infection due to the cytokine storm leading to heightened production of S1P [152, 153]. This signaling pathway induces an inflammatory phenotype and promotes angiogenesis through cooperative signaling between S1PR1 and VEGFR2, facilitating tumor vascularization [154, 155]. Elevated SphK1 expression, observed in adenocarcinomas, correlates with poor survival rates, suggesting its role in tumor development and angiogenesis regulation [156–159]. Thus, the activation of sphingolipid rheostat signaling in COVID-19 patients not only induces inflammation but also contributes to angiogenesis, linking it to cancer growth and progression.

Recent research suggests a potential link between SARS-CoV-2 proteins (M, N and S) and promotion of metastasis. The M protein, for instance, upregulates EMT-associated genes and tumor-promoting cytokines, enhancing invasiveness in breast cancer cells [160]. Co-culture studies reveal that M protein-treated aggressive breast cancer cells induce ACE2 expression in non-aggressive cells, potentially enhancing their susceptibility to SARS-CoV-2 infection and promoting aggressiveness. This bidirectional signaling may create a positive feedback loop, contributing to cancer progression and metastasis [84]. However, more studies

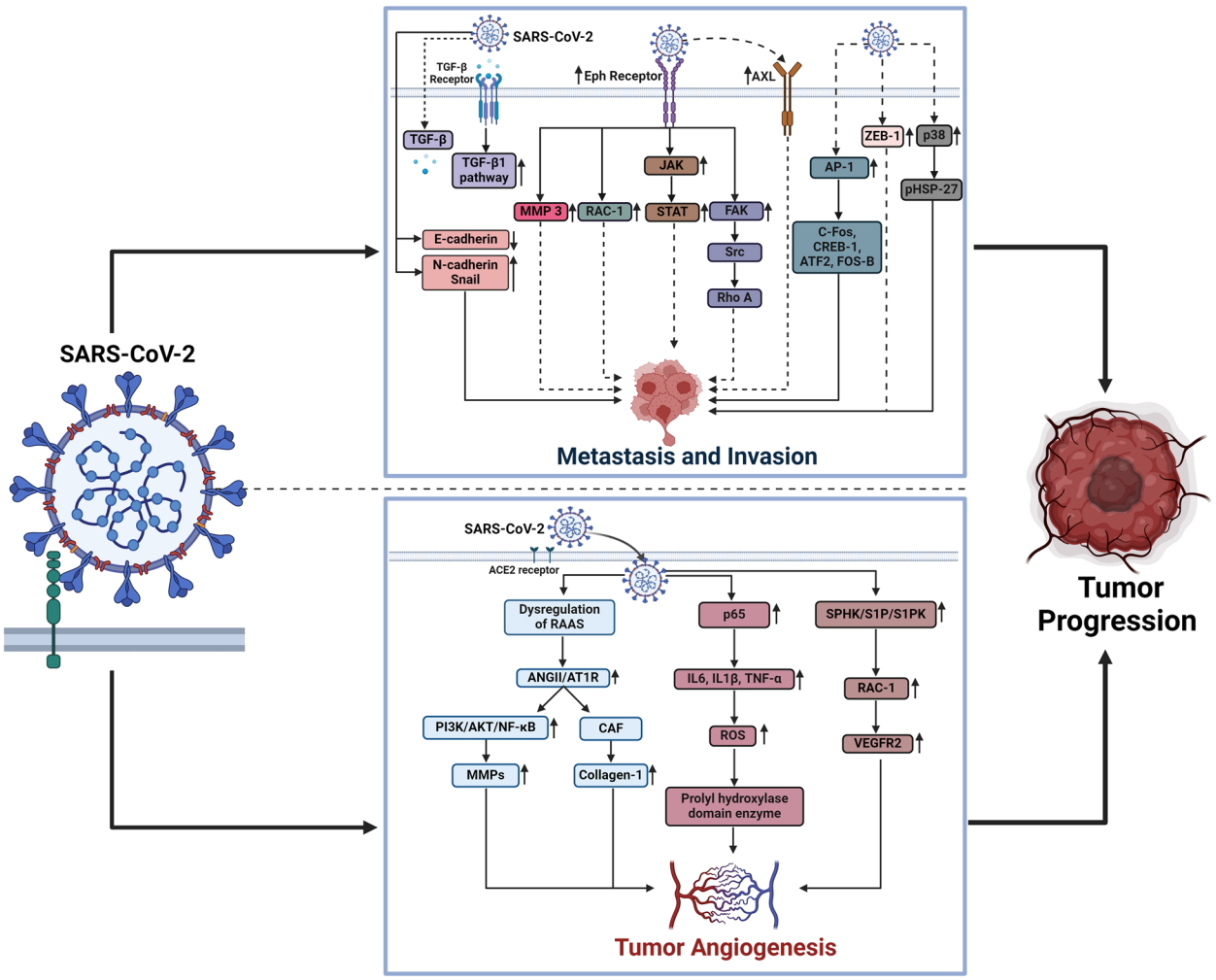


Fig. 4 The alterations in mechanisms within normal cells infected with SARS-CoV-2, drawing parallels to changes observed in cancer cells. The figure emphasizes the relationship of the alterations to key cancer-related processes, including metastasis, invasion and angiogenesis. Specific pathways and molecular changes induced by SARS-CoV-2 infection that mirror oncogenic transformations are highlighted. FAK, Focal Adhesion Kinase; MMPs, Matrix Metalloproteinases; ATF2, Activating Transcription Factor 2; AP1, Activator Protein 1; MYC, Myelocytomatosis oncogene; SPHK, Sphingosine Kinase; S1P, Sphingosine-1-Phosphate; S1PK, Sphingosine-1-Phosphate Kinase. This image was created using BioRender software

are needed to validate such findings and understand the underlying molecular mechanisms.

The S protein of SARS-CoV-2, with its NXT/S motifs, is implicated in breast cancer metastasis by upregulating Snail, a key transcription factor in the EMT process [161]. The gamma variant of spike protein, with additional NXT/S motifs, enhances protein stability and activates NF-κB signaling, augmenting breast cancer metastatic potential [162]. Moreover, the spike protein stimulates Eph receptors, activating metastasis-related molecules and pathways like RAC-1, MMP-3, JAK-STAT and FAC, suggesting its involvement in promoting metastasis [41]. Additionally, SARS-CoV-2 infection increases the expression of ZEB-1 and AXL-1, known oncogenic drivers associated with EMT, further highlighting the impact of the virus on cancer-related processes [163]. In another study, colon cancer cells stimulated with S and N protein peptides showed enhanced invasive capabilities via TGF beta 1 pathway regulation [164]. The N protein is also shown to activate the AP-1 pathway that is closely linked to cancer development [165–167]. Additionally, S protein downregulates E-cadherin while upregulating N-cadherin and Snail protein, promoting a more aggressive phenotype in breast cancer cells [161]. Evidence suggests significant upregulation of phosphorylated p38 kinase and its downstream targets, including MAPK-2 and HSP-27, during SARS-CoV-2 infection [168]. Phosphorylated HSP-27 promotes metastasis across various cancer types,

indicating a potential role for SARS-CoV-2 in activating the p38 MAPK cascade and promoting metastasis [67]. Overall, the M, N and S proteins of SARS-CoV-2 have shown the ability to influence crucial factors in inducing EMT. This includes upregulating mesenchymal markers and activating EMT-associated pathways like TGF beta 1 and NF-κB. These molecular interactions underscore the potential of the virus to enhance metastatic events within host cells. Nevertheless, more studies are needed to elucidate the impact of SARS-CoV-2 infection on cancer progression and metastasis.

NLRP3 Inflammasomes

NLRP3 is a well-known pattern recognition protein (PRR) and is a key component of the innate immune system and is known to sense cellular stress and infection. It plays a significant role in the initiation of inflammatory responses by activating caspase-1 and facilitating the release of proinflammatory cytokines like IL-1β and IL-18. Dysregulation of NLRP3 inflammasome function has been linked to tumor development, suggesting its involvement in tumorigenesis. Interestingly, SARS-CoV-2 by the interaction through N protein results in the activation of NLRP3 inflammasomes and contributes to major aspects of cancer biology including inflammation, immune response, angiogenesis, cell proliferation and metastasis (Fig. 5) [169]. Additionally, dysregulation of the RAAS can also trigger this activation, promoting the assembly and activation of the inflammasome [170, 171]. Activated NLRP3 inflammasomes lead to the secretion of IL-1β, which plays a significant role in proliferative signaling in cancers such as breast, colon, gastric, glioma, head and neck, lung, leukemia and particularly in melanoma [169]. Furthermore, the secreted IL-1β triggers the production of additional proinflammatory cytokines, such as IL-6, IL-8, IL-10, TNF-α and CXCL10, leading to a cytokine storm further resulting in inflammation induced carcinogenesis that has been observed in various cancers including head and neck carcinoma [172]. This storm not only enhances tumor proliferation and inflammation but also supports tumor survival and metastasis through signaling pathways associated with proliferation and metastasis, such as phosphorylated AKT, ERK1/2, CREB and Snail [173, 174].

Moreover, previous studies have shown that NLRP3 activation promotes angiogenesis by inducing VEGF expression through IL-1β secretion [175]. It also aids immune evasion by upregulating PD-L1 and polarizing M2 macrophages, and contributes to genomic instability by causing DNA damage in cancers like lung and skin cancer. Additionally, NLRP3 activation supports metabolic reprogramming, including the Warburg effect, by stabilizing HIF-1α and increasing glycolysis and mitochondrial ROS production [169]. Hence, overactivation of NLRP3 inflammasome through mechanisms involving SARS-CoV-2 N protein or the dysregulated RAAS system is a significant alteration that can contribute to major critical signaling of cancer intiation and development.

Conclusions

As the world continues grappling with the repercussions of the COVID-19 pandemic, the evolution of more infectious mutant viral strains is further impacting lives globally. The correlation of COVID-19 and cancer poses significant challenges, as cancer patients are immunocompromised and more susceptible to viral infections. This dual burden has spurred extensive research to understand the correlation between the two diseases and to develop suitable therapeutic strategies.

Reports have shown that SARS-CoV-2 proteins, such as the M protein, non-structural proteins, and spike protein, influence cellular functions relevant to cancer progression. These proteins can inhibit tumor suppressor genes, activate survival signaling pathways, stimulate cytokine production, and activate the NF-κB pathway, creating a tumorigenic environment. Additionally, SARS-CoV-2 proteins can promote metastasis by upregulating mesenchymal markers and metastasis-related signaling pathways. They have the ability to alter metabolic pathways, cause damage to DNA, and inhibit DNA repair systems, which can result in genomic instability and metabolic reprogramming that are specific to cancer cells. These viral proteins also influence programmed cell death evasion and aid immune evasion through upregulation of PD-L1 and M2 macrophage polarization. COVID-19 is further linked with epigenetic modifications induced by SARS-CoV-2, such as DNA methylation and histone deacetylation, that further may lead to changes in gene expression associated with cancer development. The activation of NLRP3 inflammasomes by SARS-CoV-2 intersects with multiple cancer hallmarks, suggesting a role in cancer development and progression. Nevertheless, most of these findings are based on bioinformatics and in vitro studies, necessitating further in vivo and clinical investigations to determine their clinical significance.

Recent studies have revealed that both SARS-CoV-2 and tumor cells utilizes similar mechanistic pathways to their advantage. These include inducing immunosuppression, oxidative stress, disrupting DDR signaling, activating stemness pathways, and downregulating tumor suppressor proteins. Additionally, the potential reactivation of latent oncogenic viruses in COVID-19 patients could elevate cancer risk. Consequently, it is essential to monitor individuals infected with SARS-CoV-2,

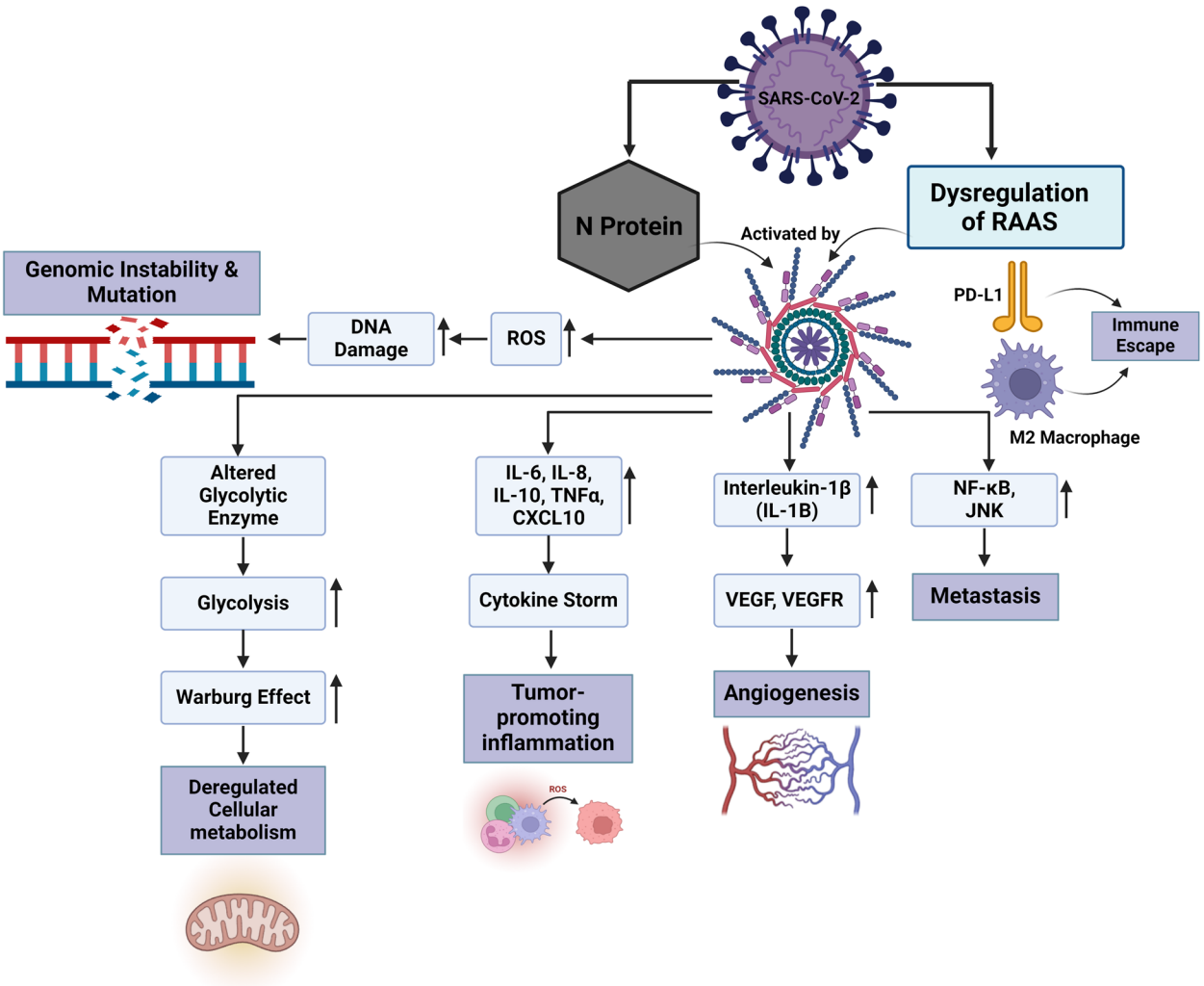


Fig. 5 Schematic diagram showing the activation of NLRP3 inflammasomes by the N protein of SARS-CoV-2 and the dysregulation of the Renin–Angiotensin–Aldosterone System (RAAS). The activation of NLRP3 led to the cancer-causing hallmarks. The figure details how these pathways contribute to processes such as deregulated cellular metabolism, tumor-promoting inflammation, inducing angiogenesis and metastasis. This image was created using BioRender software

particularly those with chronic cases, for signs of cancer development. Conversely, cancer patients are more vulnerable to SARS-CoV-2 and at higher risk of severe COVID-19 symptoms and related complications. Identifying and targeting common pathways between COVID-19 and cancer could lead to treatments that address both diseases. Despite the pandemic, timely diagnosis, treatment, and monitoring of cancer patients remain essential.

In summary, SARS-CoV-2 possesses oncogenic potential, impacting multiple hallmarks of cancer through its proteins and interactions with cellular pathways. While additional investigations are necessary to validate these findings and determine their clinical significance, understanding the relationship between COVID-19 and cancer risk is crucial for future research and therapeutic interventions.

Future perspective

Comprehensive surveillance and monitoring are necessary to address the long-term influence of COVID-19 on cancer, especially for those who have been suffering COVID symptoms for a long time, since they may be more susceptible to the cancer risk. Regular screening, including biomarker testing and imaging studies, can facilitate early detection and timely intervention. Integrating comprehensive surveillance protocols into healthcare systems is essential, especially for high-risk groups such as cancer patients and individuals with

pre-existing conditions. Digital health tools, including telemedicine can play a critical role in diagnosing and monitoring cancer risk in COVID-19 or post-acute sequelae of SARS-CoV-2 (PASC) patients by enabling remote consultations, digital screenings, and continuous monitoring of cancer-related biomarkers. Through digital tools like mobile applications, wearables, and AI-driven algorithms, patients can undergo regular health assessments, participate in personalized cancer screening programs, and receive real-time alerts for any concerning changes [176]. Furthermore, advancements in artificial intelligence (AI) and machine learning (ML) are transforming the management of long-COVID and its potential oncogenic effects. AI-driven predictive models can analyze large datasets to identify patterns and predict disease outcomes, helping stratify patients based on risk levels and personalize monitoring plans [177]. The discovery of specific biomarkers associated with chronic inflammation, immune dysregulation, and oncogenic pathways has paved the way for precision medicine approaches in managing long-COVID and cancer. These approaches enable early detection and targeted interventions, improving treatment outcomes and reducing the risk of cancer progression in post-COVID-19 patients. Another non-invasive technique is liquid biopsy technologies, particularly cfDNA analysis, that could play a pivotal role in monitoring and surveillance of cancer risk in PASC patients. Given the chronic inflammation and immune dysregulation associated with PASC, there may be an elevated risk of cancer development over time. Liquid biopsy allows for real-time monitoring of molecular changes, making it possible to detect early signs of malignancy before they become clinically apparent. This approach could enable personalized surveillance strategies, allowing for timely interventions and potentially improving long-term outcomes in PASC patients [178]. Additionally, by integrating liquid biopsy with advanced genomic tools like NGS, clinicians could identify specific mutations or alterations associated with higher cancer risk in this population, leading to more targeted and proactive cancer prevention efforts.

Immunotherapy is yet another valuable tool for monitoring and diagnosing cancer risk in PASC patients by targeting the immune dysregulation seen in both COVID-19 and cancer. By monitoring the immune parameters, like, cytokines, T cell exhaustion, and lymphopenia that is also seen in severe COVID-19 cases including PASC patient, it may be possible to detect early signs of immune-related abnormalities that could indicate a heightened cancer risk [179, 180]. Therefore, immunotherapy offers a dual role in both managing the immune aftermath of COVID-19 in PASC patients and potentially providing early diagnostic indicators for cancer risk, making it a critical tool in the post-COVID-19 landscape.

Abbreviations

ACE2	Angiotensin-Converting Enzyme 2
AKT	Protein Kinase B
ANGII/AT1R	Angiotensin II/Angiotensin II Type 1 Receptor
AP1	Activator Protein 1
ATR	Ataxia Telangiectasia and Rad3-Related Protein
BAK	BCL2 Antagonist/Killer
BRD4	Bromodomain-containing protein 4
CAFs	Cancer-Associated Fibroblasts
CHK1	Checkpoint Kinase 1
COX-2	Cyclooxygenase 2
CREB	CAMP Response Element-Binding Protein
C-RAF	RAF Proto-Oncogene Serine/Threonine-Protein Kinase
DDR	DNA Damage Response
DNMT-1	DNA Methyltransferase 1
EMT	Epithelial-Mesenchymal Transition
Eph receptor	Ephrin Receptor
ERK1/2	Extracellular Signal-Regulated Kinase 1/2
FAK	Focal Adhesion Kinase
HIF1-α	Hypoxia-Inducible Factor 1-Alpha
HLA-C	Human Leukocyte Antigen C
HSP27	Heat Shock Protein 27
HSPA1L	Heat Shock Protein A1-like
IFN-IRF1	Interferon Regulatory Factor 1
IL-1	Interleukin-1
IL-1-β	Interleukin-1-Beta
JAK/STAT	Janus Kinase/Signal Transducer and Activator of Transcription
MAPK	Mitogen-Activated Protein Kinase
MCL-1	Myeloid Cell Leukemia 1
MHC	Major Histocompatibility Complex
MMPs	Matrix Metalloproteinases
MYC	Myelocytomatosis Oncogene
NF-κB	Nuclear Factor Kappa B
NLRP3	NOD-Like Receptor Protein 3
NSP	Non-Structural Protein
ORF	Open Reading Frame
PASC	Post-Acute sequelae of SARS-CoV-2
PD-L1	Programmed Death-Ligand 1
pRB	Retinoblastoma Protein
PRR	Pattern Recognition Receptor
RAAS	Renin–Angiotensin–Aldosterone System
RAC-1	Ras-Related C3 Botulinum Toxin Substrate 1
ROS	Reactive Oxygen Species
S1P	Sphingosine-1-Phosphate
S1PK	Sphingosine-1-Phosphate Kinase
SIRT5	Sirtuin 5
SphK	Sphingosine Kinase
TGF-β	Transforming Growth Factor-Beta
TGFR	Transforming Growth Factor Receptor
TLR2	Toll-Like Receptor 2
TNF-α	Tumor Necrosis Factor-Alpha
TUB1AC	Tubulin Alpha
VEGF	Vascular Endothelial Growth Factor
VEGFR2	Vascular Endothelial Growth Factor Receptor 2
ZEB-1	Zinc Finger E-Box Binding Homeobox 1

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Authors' contributions
AJ: Manuscript draft, literature search, Art work/Figures; SS: Art work/Figures; HRK, RC, RPS: Manuscript reviewing and editing; RPS: Overall supervision and resources.

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Human and Animal Rights and Informed Consent: This article does not contain any original data but has reviewed the data with human or animal subjects performed by others.

Competing interests
The authors declare no competing interests.

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