Review

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SARS-CoV-2 Infection and Vaccination, Immune Dysregulation, and Cancer

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection elicits highly heterogeneous immune responses that influence both acute disease severity and long-term immunological outcomes. While effective antiviral immunity leads to viral clearance in many individuals, a subset develops persistent immune dysregulation characterized by chronic inflammation, immune exhaustion, and impaired tissue repair, hallmarks of long COVID. These immune alterations are parallel to established mechanisms of carcinogenesis and tumor progression, including sustained cytokine signaling, oxidative stress, metabolic reprogramming, and disruption of antitumor immune surveillance. Emerging evidence suggests that SARS-CoV-2 may further interact with cancer biology through direct or abortive infection of tumor or stromal cells, as well as through viral protein–mediated activation of oncogenic and inflammatory signaling pathways such as NF-κB, MAPK/ERK, JAK/STAT3, and Toll-like receptor signaling. In addition, immune evasion strategies observed in both chronic viral infection and cancer, including immune checkpoint upregulation, impaired antigen presentation, and the establishment of immunosuppressive microenvironments, may be reinforced following SARS-CoV-2 infection. SARS-CoV-2 vaccination limits severe disease and persistent immune activation, thereby potentially mitigating long-term tumor-permissive immune states without evidence of oncogenic risk. These observations position SARS-CoV-2 infection as a non-classical but biologically relevant modifier of cancer-associated immune landscapes. Elucidating the long-term consequences of post-infectious immune remodeling will be essential for defining cancer risk, optimizing surveillance strategies, and informing therapeutic interventions in COVID-19 survivors.

Keywords: SARS-CoV-2; COVID-19; vaccination; immune dysregulation; chronic inflammation; cancer

1. Introduction

The emergence of Coronavirus Disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has presented a global health challenge with far-reaching consequences on public health systems and individual physiological well-being. Beyond its immediate acute respiratory manifestations, a growing body of evidence indicates that SARS-CoV-2 infection can lead to long-term immunological sequelae, fundamentally altering host immune responses and potentially exacerbating pre-existing conditions or contribute to novel pathologies [1]. The interplay between viral infection, immune evasion, and carcinogenesis is well established in oncology. Chronic viral infections have long been recognized as significant etiological drivers of various malignancies, establishing a precedent for investigating SARS-CoV-2 in a similar oncogenic framework [2]. Mechanistically, chronic viral infections drive sustained inflammation, dysregulate immune response, thereby establishing a biological context permissive for malignant transformation [3]. These same processes are documented in COVID-19, where persistent cytokine production, oxidative stress, and immune exhaustion may collectively contribute to a pro-tumorigenic milieu [4]. Understanding how SARS-CoV-2 intersects with cancer biology is essential for evaluating long-term

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risks and informing surveillance strategies for post-COVID populations. Because the long-term consequences of SARS-CoV-2 infection are dictated by early immune dynamics that control the resolution or persistence of inflammation, an understanding of the acute and chronic immune responses to SARS-CoV-2 is necessary for assessing downstream immune dysfunction with potential relevance to carcinogenesis.

2. Acute and Chronic Immune Responses to SARS-CoV-2

SARS-CoV-2 infection elicits a broad spectrum of immune responses that range from well-coordinated antiviral activity in asymptomatic individuals to profound dysregulation in severe disease [5]. The early immune responses influence the transition from acute infection to long-term inflammatory sequelae and are increasingly recognized as key determinants of chronic pathology, including immune exhaustion, persistent inflammation, and impaired tissue repair.

2.1. Acute Immune Activation and Cytokine Storm

Acute SARS-CoV-2 infection initiates a rapid antiviral response in the airway epithelium, macrophages, and dendritic cells, driven by pattern-recognition receptors (PRRs) that detect viral RNA and structural proteins [6]. This early sensing induces type I and III interferons (IFNs) and a coordinated release of pro-inflammatory cytokines, forming the first line of antiviral defense [6]. In severe COVID-19, however, this IFN response is blunted and delayed [7], leading to compensatory surge in Nuclear Factor-kappa B (NF-κB)–driven inflammatory cytokines, such as interleukin (IL)-6, IL-1β, Tumor Necrosis Factor (TNF)-α, Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF). A range of chemokines are also disproportionately amplified, resulting in extensive leukocyte recruitment, lung infiltrates, and tissue injury [8]. Excessive activation of monocytes and macrophages, neutrophils, including the induction of neutrophil extracellular trap (NET) formation through NETosis, a form of neutrophil cell death characterized by nuclear disassembly and release of chromatin and modified proteins that trap microorganisms and promote inflammation, and T cells fuels systemic inflammation [9], endothelial damage, and coagulopathy, contributing to the progression toward Acute Respiratory Distress Syndrome (ARDS) and multi-organ dysfunction [10]. The cytokine storm or Cytokine Release Syndrome (CRS) in COVID-19 represents an acute, uncontrolled hyper-inflammatory state characterized by markedly elevated circulating cytokines, widespread tissue injury, and high mortality [11]. Unlike a physiological antiviral response, CRS involves sustained, self-amplifying cytokine production that becomes pathogenic, driving vascular leak, shock, and multi-organ failure [11,12]. Severe COVID-19 consistently features elevated serum levels of IL-6, IL-1β, TNF-α, IL-2, IL-7, IL-8, IL-10, GM-CSF, Interferon Gamma-Induced Protein (IP)-10 (CXCL10), Monocyte Chemoattractant Protein (MCP)-1 (CCL2), MCP-3 (CCL7), and IL-17, with IL-6 emerging as a central biomarker of hyperinflammation [14]. Major cellular contributors include macrophages and monocytes, neutrophils, activated T cells, Natural Killer (NK) cells, and endothelial and epithelial cells, which collectively amplify inflammation and promote alveolar injury, edema, and ARDS [15].

The cytokine storm arises from the convergence of multiple upstream signaling pathways. SARS-CoV-2 binding down-regulates Angiotensin-Converting Enzyme 2 (ACE2), increasing Angiotensin (Ang) II–Angiotensin type 1 receptor (AT1R) signaling and activating Tumor Necrosis Factor-α–Converting Enzyme (TACE) also known as Disintegrin and Metalloprotease 17 (ADAM17) [16]. This promotes ACE2 shedding and release of TNF-α and soluble Interleukin 6 Receptor α (IL-6Rα). TNF-α and Epidermal Growth Factor Receptor (EGFR) ligands activate NF-κB, while IL-6/sIL-6Rα activates Janus Kinase/Signal Transducers and Activators of Transcription (JAKSTAT)3 signaling pathway [17], forming a synergistic IL-6 amplification loop that drives massive cytokine production and ARDS [16]. Viral RNA and proteins could also activate Toll Like Receptors (TLRs) and cytosolic sensors, inducing NF-κB–dependent cytokines (IL-6, IL-1β, TNF-α) and chemokines that recruit inflammatory leukocytes to the lung [18]. The SARS-CoV-2 spike protein can also directly activate TLR2–Myeloid Differentiation Primary response 88 (MyD88)– NF-κB signaling [19],

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inducing IL-6, IL-1β, and TNF-α in macrophages and lung epithelial cells and triggering in vivo inflammation in mouse models [19]. IL-6 cis- and trans-signaling through membrane-bound or soluble IL-6R engages glycoprotein (gp)130–JAK–STAT3 pathway [20], amplifying production of IL-6, IL-8, MCP-1 (CCL2), Vascular Endothelial Growth Factor (VEGF), and other mediators that increase vascular permeability, leukocyte recruitment, and lung dysfunction [20]. Excess cytokines drive endothelial activation, vascular leak, coagulopathy, shock, and multi-organ failure [12]. In the lung, IL-6-centered inflammation and leukocyte infiltration cause diffuse alveolar damage, hypoxemia, and ARDS, which is the primary cause of mortality in severe COVID-19 [8].

2.2. Transition from Acute to Chronic Immune Dysregulation

Acute SARS-CoV-2 infection is characterized by intense innate and adaptive immune activation [21], but in a subset of individuals this hyperinflammatory state evolves into persistent, dysregulated immunity rather than resolving fully [21,22]. Longitudinal and mechanistic studies now show that early hyperactivation, antigen persistence, and discriminated adaptive responses shape the long-term immune pathology observed in long COVID post-acute sequelae [23,24]. These trajectories reveal a shift from an initially protective antiviral response toward a chronic state marked by ongoing inflammation, altered cytokine patterns, and features of immune exhaustion or suppression.

Long-term biomarker studies demonstrate that although many inflammatory mediators decline over time, they often remain abnormal compared with non-COVID respiratory infections [26]. In a six-month longitudinal cohort, only a few markers such as Macrophage Inflammatory Protein (MIP)-1β (CCL4) at three months and Cystatin D (CST5) at six months remained elevated, while many inflammatory proteins, including CXCL1, CXCL5/6, IL-7, Programmed Cell Death Ligand 1 (PD-L1), and Tumor Necrosis Factor Ligand Superfamily Member 14 (TNFSF14), were reduced relative to controls, suggesting a transition from low-grade inflammation toward immune suppression or exhaustion, particularly in long-COVID individuals [26]. At twelve months, individuals with pulmonary sequelae or long COVID continued to exhibit elevated antimicrobial and immune-cell activation proteins, chemokines such as Macrophage Inflammatory Protein (MIP)-1α (CCL3) and Macrophage Inflammatory Protein (MIP)-3 (CCL20), and increased IFN-γ, indicating chronic chemokine-driven immune cell recruitment and persistent tissue involvement [27]. Additional studies report long-term reductions in granulocytes, monocytes, and lymphocyte subsets (T, B, NK cells), along with a Th1→Th2 cytokine shift ten months post-infection, consistent with impaired antiviral capacity and altered inflammatory pattern [28].

Across multiple cohorts, acute hyperinflammation does not simply resolve but transitions into a state of simultaneous chronic activation and immunosuppression [21]. Reviews and longitudinal analyses describe persistent activation of neutrophils (including NETosis) monocytes, mast cells, and NK cells for up to 8–15 months, suggesting reprogramming of bone-marrow progenitors and sustained innate hyperreactivity [21,22]. Convalescent and long-COVID patients also exhibit lasting T-cell activation and exhaustion phenotypes, including increased expression of T Cell Immunoglobulin Mucin (TIM)-3, T Cell Immunoglobulin and ITIM (immunoreceptor tyrosine-based inhibitory motif) domain (TIGIT), and PD-1 during early convalescence, exhausted SARS-CoV-2-specific $CD8^+$ T cells and skewed $CD4^+$ subsets at eight months [29], and reduced naïve T- and B-cell pools with enrichment of inflammatory memory subsets across multiple cohorts [28,29].

Multi-omics profiling further reveals uncoordinated adaptive immunity in long COVID, with systemic inflammation, increased $CD4^+$ T cells primed for tissue homing [29], exhausted virus-specific $CD8^+$ T cells, elevated SARS-CoV-2 antibody levels, and poor coordination between T- and B-cell responses [29], all of which suggest ongoing antigenic stimulation and failed immune resolution [24]. Reviews integrating these findings propose that persistent viral antigen or RNA acts as a chronic stimulus that maintains immune activation [25]; when inadequately down-regulated, this shifts the host response from protective antiviral immunity toward dysregulated, tissue-damaging inflammation and autoimmunity [25]. These data show that the transition from acute to chronic immune dysregulation in COVID-19 reflects a complex interplay between residual inflammation,

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persistent innate activation, maladaptive T- and B-cell responses, and features of immune exhaustion. These mechanistic trajectories underpin the immunopathology of long COVID and have important implications for chronic inflammatory and oncogenic processes.

2.3. Persistent Inflammation and Immune Remodeling in Long COVID

Persistent inflammation is a defining immunological feature of long COVID, with many individuals exhibiting ongoing, low-grade inflammatory activity for months to more than a year after acute infection [25,30]. Rather than representing a simple continuation of the acute hyperinflammatory phase, this chronic state reflects a complex mixture of residual cytokine elevation, immune dysregulation, and features of exhaustion or impaired resolution [22], producing a heterogeneous but biologically coherent post-acute inflammatory phenotype [32].

Long-COVID cohorts consistently demonstrate sustained elevation of IL-6, IL-1β, TNF-α, IFN-γ, IL-17, and chemokines such as CCL2, CXCL10, and Macrophage Inflammatory Protein (MIP)-1β (CCL4), with abnormalities detectable up to 6–12 months after infection [33]. These cytokine patterns indicate a chronic inflammatory milieu that distinguishes long COVID from fully recovered individuals. Several studies report diffuse, abnormal cytokine signatures persisting for at least eight months, suggesting that inflammatory circuits remain active long after viral clearance. A Singapore cohort further identified elevated IL-17A, IL-12p70, IL-1β, and angiogenic mediators at six months [34], with CCL2 and Platelet-Derived Growth Factor (PDGF)-BB particularly enriched in symptomatic individuals, pointing to ongoing inflammation coupled with vascular remodeling [34].

Cellular analyses reinforce this picture of persistent immune activation. Long-COVID patients exhibit highly activated monocytes, alongside activated T cells, loss of naïve T- and B-cell subsets, and expansion of exhausted or terminal effector populations [28,32]. These cellular abnormalities frequently coexist with elevated inflammatory cytokines and chemokines, indicating a state of chronic immune activation connected with immune dysregulation [35]. Specific clinical phenotypes, such as long COVID with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)-like features, show increased neutrophils and monocytes, high pro-inflammatory cytokines, elevated Galectin (Gal)-9 and Artemin (ARTN), and the presence of autoantibodies, suggesting a convergence of innate activation, immune exhaustion, and autoimmune processes [36].

Persistent inflammation also correlates with the hallmark symptoms of long COVID, including fatigue, post-exertional malaise, cognitive dysfunction (“brain fog”), dysautonomia, dyspnea, and chronic pain [31]. Mechanistic links include neuroinflammation, microclot-associated hypoperfusion, and immunothrombosis, all of which can impair tissue oxygenation and neural function [37]. Extracellular-vesicle–associated proinflammatory cytokines, including IL-6, TNF-α, IL-1β, CXCL10, and CCL2, as well as neuronal injury markers such as Neurofilament Light chain (NfL), Glial Fibrillary Acidic Protein (GFAP) detected 15 months post-infection further suggest ongoing neuroinflammatory and neurodegenerative processes, even in cases where plasma cytokines appear to normalize [38,39]. These findings indicate that long COVID is characterized by persistent but heterogeneous inflammation, marked by sustained elevations in IL-6, IFNs, chemokines, and tissue-injury markers, as well as activated innate and adaptive immune cells [35]. This chronic inflammatory state, often accompanied by immune exhaustion, autoimmunity, and microvascular injury, appears central to the persistence of symptoms and the development of long-term organ dysfunction. Notably, SARS-CoV-2 vaccination prior to or following infection has been associated with reduced severity of long COVID–associated immune dysregulation, suggesting that vaccine-induced immune priming may limit the duration and magnitude of chronic inflammatory responses [40].

2.4. T-Cell Dysfunction, Exhaustion and Impaired Immune Surveillance

Acute and post-acute SARS-CoV-2 infection is characterized by both quantitative and qualitative impairments in T-cell immunity [38,39]. Many patients exhibit a pronounced loss of circulating T cells together with an “exhaustion-like” phenotype marked by elevated inhibitory receptors, skewed

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differentiation states, and diminished effector functions [38,40]. These abnormalities can persist for months after infection and are increasingly implicated in the pathogenesis of long COVID [44].

T-cell exhaustion in COVID-19 reflects a constellation of functional and molecular defects [45]. Exhausted T cells demonstrate reduced proliferative capacity and cytokine production, sustained expression of inhibitory receptors such as PD-1, TIM-3, Lymphocyte activation gene (LAG)-3, and Cytotoxic T-lymphocyte-associated protein (CTLA)-4, and transcriptional and epigenetic reprogramming accompanied by metabolic dysfunction [42,43]. During acute disease, total T-cell counts, including $CD4^+$ and $CD8^+$ subsets, are markedly reduced, and the remaining T cells frequently upregulate PD-1 and TIM-3, particularly in critically ill patients [38,44]. Low T-cell counts correlate strongly with mortality, and severe cases accumulate terminally differentiated or senescent $CD28^-CD57^+$ and Terminally Differentiated Effector Memory (TEMRA)/effector-memory T cells expressing PD-1, indicating a shift toward an exhausted or senescent effector state [38,40].

Interpretation of these phenotypes remains complex, as co-inhibitory receptor expression can also reflect strong activation rather than true exhaustion [39,45]. Functional assays in some cohorts show preserved or even heightened cytokine production despite high PD-1 or TIM-3 expression [42], underscoring the need for stringent criteria to define bona fide exhaustion [45]. Reviews emphasize that true exhaustion requires convergent evidence: sustained inhibitory-receptor expression, impaired effector function, distinct transcriptional and epigenetic signatures, and persistent antigenic stimulation [42,46]. Consistent with this, several studies argue that not all COVID-19 cases exhibit pathological exhaustion; instead, many patients display hyperactivated T cells that merely express exhaustion-associated markers [50].

Long-term follow-up studies reveal that T-cell dysfunction can persist well beyond the acute phase [41,48]. Individuals recovering from severe COVID-19 show reduced naïve T-cell pools and expanded exhausted or senescent $CD8^+$ subsets, including $CD57^+$ and $PD\text{-}1^+$ populations, up to six months after infection, often accompanied by unresolved inflammation [51]. Long-COVID cohorts exhibit exhausted SARS-CoV-2-specific $CD8^+$ T cells, dysregulated $CD4^+$ T-cell trafficking, and poorly coordinated T and B cell interactions [28,49], suggesting ongoing antigenic stimulation and maladaptive memory formation [23]. Circulating markers of T-cell activation and exhaustion, including soluble CD25, TIM-3, and LAG-3, correlate with persistent dyspnea, fatigue, and cognitive symptoms up to 18 months after mild infection, indicating that T-cell dysregulation contributes directly to long-term clinical manifestations [53]. These findings show that COVID-19 drives a continuum of T-cell abnormalities from acute lymphopenia and hyperactivated, exhaustion-marked T cells to long-lasting pools of exhausted or senescent memory cells, particularly after severe disease or in long COVID-19. Whether these states represent irreversible exhaustion or a mixed activation–dysfunction phenotype remains debated, but the persistence of inhibitory-receptor-high, poorly regenerative T-cell compartments likely contributes to impaired viral control, increased susceptibility to reinfection, and chronic symptomatology [53]. All these persistent T cell dysfunctions suggest a state of impaired immune surveillance that may extend to tumor tissues, providing a rationale to examine whether SARS-CoV-2 can directly infect or modulate cancer cells and the tumor microenvironment.

3. SARS-CoV-2 Infection of Cancer Cells

Although the systemic immune effects of SARS-CoV-2 infection are well characterized, its direct interactions with malignant cells and tumor tissues have only recently gained attention. Tumors exhibit altered receptor expression, impaired antiviral signaling, metabolic stress, and immunosuppressive microenvironments that may increase susceptibility to viral entry, persistence, or infection-induced phenotypic remodeling. Emerging experimental and clinical evidence indicates that SARS-CoV-2 can infect or modulate selected cancer cell types via both ACE2-dependent and alternative entry pathways, raising questions about tumors as potential viral reservoirs and the consequences for tumor behavior and the tumor microenvironment.

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3.1. Evidence for Direct or Abortive Infection of Cancer Cells

SARS-CoV-2 has been shown to directly infect several human cancer cell types in vitro [51,52], raising important questions about whether tumors may act as permissive viral reservoirs and how infection might influence tumor biology. Human hepatoma cell lines such as Huh7.5 and HepG2 support productive viral replication [54] with marked cytopathic effects, whereas non-transformed liver progenitors and stellate cells remain non-permissive [54], indicating that malignant transformation and altered innate signaling shape susceptibility. Serial passage of SARS-CoV-2 in Huh7.5 cells selects spike-adapted variants, including E484D, P812R, Q954H, and Δ68-76 that replicate more efficiently in hepatoma and lung cancer lines, demonstrating that tumor-associated environments can drive viral adaptation and reduce dependence on canonical ACE2 entry pathways [53,54]. In glioblastoma, certain high-grade, low-passage lines also support efficient infection, with permissiveness linked to elevated ACE2 expression and impaired interferon responses [54]. Engineered U87 glioma cells overexpressing ACE2 become highly permissive, confirming receptor-dependent entry in this context [58]. Notably, several hepatoma-adapted and E484D-bearing variants can partially bypass ACE2 [57] by exploiting alternative receptors such as Asialoglycoprotein Receptor (ASGR)1, Dendritic Cell-Specific Intercellular adhesion molecule-Grabbing Non-integrin (DC-SIGN), and Transmembrane Protein (TMEM)106B, or by using heparan-sulfate–dependent mechanisms [59], revealing ACE2-independent routes that may be particularly relevant in cancer cells.

Beyond direct infection, SARS-CoV-2 exposure can induce phenotypic remodeling in tumor cells: HepaRG progenitors undergo partial dedifferentiation despite non-productive infection and spike-induced syncytia [54]. These findings show that SARS-CoV-2 can infect or modulate multiple cancer cell types through both ACE2-dependent and alternative pathways, with potential consequences for tumor behavior, viral persistence, and cancer–COVID-19 interactions that remain incompletely understood.

3.2. Biological and Clinical Implications of Viral–Tumor Interactions

Emerging evidence suggests that tumors may function as immunologically permissive niches for SARS-CoV-2, with potential consequences for viral persistence, tumor microenvironment (TME) remodeling, and chronic inflammation. Cancer patients, particularly those with hematologic malignancies, frequently exhibit prolonged viral shedding [59,60], persistent PCR positivity, and intra-host viral evolution when $CD8^+$ T-cell immunity is impaired, consistent with tissue-based viral reservoirs.

Spatial-transcriptomics analyses have identified SARS-CoV-2 RNA and viral-response gene signatures within hepatocellular carcinoma and colorectal tumors months after infection [62], indicating localized viral persistence in malignant and adjacent tissues. Tumor-associated immunosuppression, immune-privileged niches, and disrupted antiviral signaling may further facilitate long-term viral retention [62,63].

Within the TME, viral-high regions display PD-L1 upregulation, T-cell dysfunction, and B-cell–rich immune niches, suggesting that SARS-CoV-2 can reshape local immune architecture and potentially influence responsiveness to immune-checkpoint blockade [62]. Infection-induced cytokines, including IL-6, IL-1, TNF-α, and Nucleotide-binding oligomerization domain, Leucine rich Repeat and Pyrin domain containin (NLRP)3 inflammasome activation promote pro-tumorigenic inflammation [64–66], epithelial–mesenchymal transition, angiogenesis, and immune escape, while systemic cytokine storm and long-COVID–like low-grade inflammation may further sustain a chronic inflammatory milieu conducive to tumor progression [67,68].

Persistent infection in immunocompromised hosts supports ongoing antigenic stimulation, oxidative stress, and epigenetic remodeling, all recognized drivers of tumorigenesis, and reviews have proposed that chronic SARS-CoV-2 exposure may contribute to cancer initiation, recurrence, or accelerated progression [60]. These findings suggest that tumors, especially in immunosuppressed individuals, may serve as sanctuaries for lingering SARS-CoV-2, generating a dysfunctional,

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inflammatory TME that could influence both viral persistence and cancer biology, although definitive causal evidence in patients remains limited [63,69,70].

4. SARS-CoV-2 Viral Protein–Driven Modulation of Oncogenic Signaling

Beyond whole-virus infection, individual SARS-CoV-2 proteins can directly engage host signaling networks and reprogram cellular responses in ways relevant to oncogenesis. Viral structural proteins interact with cell-surface receptors and intracellular signaling hubs, modulating pathways that govern inflammation, cell survival, stress responses, and immune evasion. In cancer cells and tumor-associated stromal and immune compartments, such protein-mediated signaling may amplify pro-tumorigenic programs independently of productive viral replication.

4.1. SARS-CoV-2 Spike (S1) Protein–Mediated Signaling and Inflammatory Crosstalk

The SARS-CoV-2 spike S1 subunit functions as a potent pro-inflammatory ligand capable of activating multiple oncogenic-relevant signaling pathways across diverse cell types [18,71,72]. In lung and intestinal epithelial cells, recombinant S1 alone triggers rapid Extracellular Signal-Regulated Protein Kinases (ERK)1/2 Mitogen-Activated Protein Kinase (MAPK) activation, p38 phosphorylation, and Activator Protein (AP)-1–driven transcription, with MEK inhibition suppressing downstream cytokine production, including IL-1β, IL-6, IL-8, and TNF-α [71,73]. Similar MAPK activation is observed in hepatoma and lung cancer lines, where S1 enhances AT1R-linked ERK signaling and promotes IL-6 release, while DC-SIGN–expressing myeloid cells exhibit preferential ERK activation without NF-κB engagement, underscoring receptor-specific signaling dynamics [73,74].

S1 also robustly activates NF-κB through TLR4 or TLR2–MyD88 pathways in macrophages, epithelial cells, and microglia, inducing p65 phosphorylation, IκBα degradation, and transcription of inflammatory mediators [18,75]. In vivo, intratracheal S1 administration produces acute lung injury with strong NF-κB activation [77], and in neural tissues S1 drives microglial activation, NLRP3 inflammasome signaling, and neuroinflammatory cytokine release [73]. Endothelial cells and cardiac fibroblasts similarly respond to S1 with NF-κB and MAPK-dependent induction of adhesion molecules, tissue factor, Transforming Growth Factor (TGF)-β1, and profibrotic mediators, linking spike exposure to vascular inflammation and remodeling [77,78]. These findings demonstrate that S1 acts as a Pathogen-Associated Molecular Pattern (PAMP)-like stimulus that engages MAPK/ERK, NF-κB, and inflammasome pathways to induce IL-6, IL-8, TNF-α, and related cytokines in a tissue-specific manner [18,71]. Because these same pathways underpin oncogenic signaling, fibrosis, and tumor-promoting inflammation, S1-driven responses provide a mechanistic bridge between SARS-CoV-2 exposure and cancer-relevant inflammatory microenvironments, even though direct oncogenic transformation by spike has not been demonstrated [65–67].

4.2. SARS-CoV-2 Membrane (M) Protein and Intracellular Stress Response

The SARS-CoV-2 membrane (M) protein exhibits oncogenic-like activity in breast cancer models, particularly in triple-negative breast cancer (TNBC), where it drives EMT, proliferation, migration, and malignant reprogramming [65,79]. In highly aggressive MDA-MB-231 cells, M protein induces strong upregulation of EMT and stemness regulators, including Twist, Zeb1, Snail, and Hypoxia-Inducible Factor (HIF)-1α, together with mesenchymal markers such as N-cadherin and vimentin, resulting in enhanced mobility, proliferation, metastatic potential, and stem-like behavior [80]. In contrast, less aggressive MCF-7 cells exhibit increased EMT transcription factors but minimal induction of mesenchymal markers, indicating a partial EMT phenotype and a weaker overall transformation [80].

Mechanistically, the M protein activates NF-κB signaling, increasing p65/p50 activity and inflammatory cytokine expression, which in turn drives EMT gene programs and migration. Pharmacologic inhibition of NF-κB with BAY11-7082 suppresses these effects, and in MDA-MB-231

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cells, NF-κB inhibition also reduces STAT3 phosphorylation, demonstrating that NF-κB lies upstream of JAK/STAT3 in M-driven signaling. Reviews of SARS-CoV-2 oncogenic mechanisms further highlight this NF-κB–JAK/STAT3 axis, linking M protein to IL-6, IL-8, TNF-α, and other cytokines that reinforce EMT and tumor aggressiveness [81].

Beyond its direct effects on TNBC cells, the M protein promotes malignant cross-talk within the tumor microenvironment. M-treated MDA-MB-231 cells can reprogram neighboring non-aggressive MCF-7 cells in co-culture, inducing migration, proliferation, and stemness through EMT and inflammatory gene activation effectively converting them toward a more aggressive phenotype [80]. Follow-up studies show that extracellular vesicles (EVs) released from M-activated TNBC cells further reprogram mesenchymal stem cells and endothelial progenitors into tumor-supportive states, enhancing migration, stemness, and metastatic behavior in non-aggressive breast cancer cells. These findings position the SARS-CoV-2 M protein as a potent modulator of TNBC aggressiveness, capable of reshaping both cancer cells and surrounding stromal populations through coordinated NF-κB–JAK/STAT3–cytokine signaling [65,80].

5. Oncogenic and Pro-Tumoregenic Pathways Activated by SARS-CoV-2

SARS-CoV-2 infection and viral protein–mediated signaling converge on host intracellular pathways that regulate inflammation, cell survival, proliferation, and immune responses—processes central to oncogenesis and tumor progression. Independent of direct viral replication, SARS-CoV-2–induced perturbations of receptor signaling, innate immune sensors, and cytokine networks can activate canonical pro-tumorigenic pathways. Among these, the MAPK/ERK cascade and inflammatory signaling axes involving NF-κB, JAK/STAT3, and Toll-like receptor 2 (TLR2) emerge as recurrent nodes linking antiviral responses to chronic inflammation, immune evasion, and tumor-permissive states.

5.1. MAPK/ERK Pathway

SARS-CoV-2 robustly activates the MAPK signaling network, particularly the ERK1/2 and p38 MAPK pathways, which are central regulators of cytokine production, cell survival, proliferation, and stress responses [81–83]. These same pathways are deeply embedded in classical oncogenic signaling, creating mechanistic intersections between viral infection, inflammation, and tumor-promoting biology [68,84]. Early during infection, SARS-CoV-2 induces rapid Raf/MEK/ERK activation [86], with ERK1/2 phosphorylation peaking within an hour in Calu-3 cells [86]. Pharmacologic MEK1/2 inhibition or ERK1/2 knockdown reduces viral replication and dampens cytokine output, demonstrating that ERK signaling supports both viral propagation and inflammatory responses. Spike-dependent mechanisms also contribute. The receptor-binding domain activates EGFR–CRAF–MEK–ERK signaling in Caco-2 cells, and inhibition of EGFR/MAPK reduces entry of both spike-pseudotyped and authentic virus [87]. Even in the absence of full viral infection, recombinant S1 alone activates ERK1/2 in lung and intestinal epithelial cells, linking structural viral proteins directly to MAPK engagement [71,74].

Parallel to ERK activation, SARS-CoV-2 strongly induces p38 MAPK signaling [83]. Phosphoproteomic studies show marked activation of p38α/β, with p38β/MAPK11 required for efficient viral replication [88]. Spike-mediated entry also triggers p38 activation, and selective p38 inhibitors reduce IL-6, IL8 (CXCL8), CXCL10, and TNF-α production in primary lung tissue and organoids while preserving interferon responses [84]. Clinical and transcriptomic analyses reveal that SARS-CoV-2 suppresses Dual-Specificity Protein Phosphatase (DUSP)1 and DUSP5, key phosphatases that normally restrain MAPK activity, thereby amplifying p38/ERK and NF-κB signaling [81,88]. MAPK activation is tightly linked to cytokine production in SARS-CoV-2 infection [72]. ERK and p38 drive expression of TNF-α, IL-6, IL-8, and CXCL chemokines in lung epithelial cells and cancer cell lines, and inhibition of either pathway reduces these inflammatory mediators [58,89]. This MAPK-driven cytokine output contributes to the systemic cytokine storm observed in severe COVID-19, a major driver of tissue injury and multi-organ pathology [7,89].

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These MAPK responses also intersect with oncogenic biology [72]. ERK1/2 regulates c-Myc and other growth-promoting genes, and elevated H-RAS, C-RAF, and MAPK1/2 expression has been reported in COVID-19 patients. Dysregulated p38 signaling supports angiogenesis, metastasis, and treatment resistance in cancer, and is disproportionately upregulated in SARS-CoV-2 infection through ACE2 loss and direct viral activation [92]. Upregulation of the MAP2K4–p38 axis is associated with EMT markers and fibrosis in COVID-19, and chronic inflammation coupled with MAPK/NF-κB activation is a well-established tumor-promoting condition [93]. This show that SARS-CoV-2 rapidly activates ERK1/2 and p38 MAPK through ACE2/AT1R, EGFR, and spike-dependent mechanisms, promoting cytokine production, viral replication, and tissue remodeling [73,85,86]. Because these same MAPK cascades regulate proliferation, survival, EMT, angiogenesis, and fibrosis, SARS-CoV-2–induced MAPK activation provides a biologically plausible link between COVID-19–associated inflammation and tumor-promoting microenvironments, even though direct oncogenic transformation by the virus has not been demonstrated [68,84].

5.2. NF-κB, JAK/STAT3 and TLR2-Mediated Innate Activation Pathways

NF-κB is a central hub linking SARS-CoV-2–induced inflammation to tumor-promoting biology [94]. As a master transcriptional regulator, NF-κB drives expression of TNF-α, IL-1β, IL-6, VEGF, cyclin D1, MYC, B cell lymphoma (BCL)-2 protein, and EMT-associated transcription factors such as Twist and Snail [92,93], molecules that collectively promote tumor initiation, survival, angiogenesis, EMT, and metastasis. Multiple SARS-CoV-2 proteins activate this pathway, including spike (S), nucleocapsid (N) through liquid–liquid phase separation with Transforming Growth Factor β-activated Kinase (TAK)1/IKK, Open reading Frame (ORF)3a, membrane (M) protein, ORF7a, and SARS-CoV-2 Nonstructural Protein (NSP)6 via TAK1–NEMO complexes [94,95]. These viral triggers converge on canonical NF-κB activation, generating a potent inflammatory transcriptional program that mirrors pathways commonly upregulated in inflammation-driven cancers.

Downstream of NF-κB, the IL-6/JAK/STAT3 axis forms a second major oncogenic signaling module engaged during SARS-CoV-2 infection [98]. IL-6 produced in response to NF-κB activates JAKs and phosphorylates STAT3, inducing genes involved in proliferation (cyclin D1), survival (BCL-xL), angiogenesis (VEGF), matrix remodeling (Matrix Metallopeptidases (MMPs)), and EMT. Importantly, NF-κB and STAT3 reinforce one another through positive feedback loops: NF-κB induces IL-6, STAT3 amplifies IL-6 and other pro-tumorigenic mediators, and both sustain chronic inflammatory circuits. This reciprocal activation is a hallmark of tumor-promoting microenvironments and is strongly implicated in cancer progression, metastasis, and immune evasion [98].

TLR2-mediated innate sensing provides the upstream trigger that links SARS-CoV-2 structural proteins to NF-κB and IL-6/STAT3 activation. Recombinant spike protein, full-length S, S1, or S2, is detected by TLR2 heterodimers (TLR2/1 or TLR2/6), initiating MyD88-dependent NF-κB activation and inducing IL-6, IL-1β, TNF-α, CXCL1/2, and CCL2 in macrophages and lung epithelial cells. These responses are abolished in Tlr2-deficient cells and mice, confirming TLR2 as a primary innate sensor of spike. The envelope (E) protein also binds TLR2 and activates NF-κB, driving robust CXCL8 production; NF-κB inhibition markedly suppresses this chemokine, whereas ERK/p38 blockade has only partial effects. Together, these findings establish the spike (S)/envelop (E) → TLR2–MyD88–NF-κB axis as a core driver of SARS-CoV-2–induced cytokine storm and a mechanistic bridge to IL-6/JAK/STAT3 activation. Together, NF-κB, JAK/STAT3, and TLR2 signaling form an integrated inflammatory network that is strongly associated with tumor-promoting processes [98]. SARS-CoV-2 proteins activate TLR2-MyD88 to initiate NF-κB–driven cytokine production, which in turn fuels IL-6/STAT3 signaling and reinforces chronic inflammatory loops [19]. In oncologic contexts, these pathways are tightly linked to EMT, angiogenesis, metastasis, immune evasion, and tumor cell survival. Although SARS-CoV-2 is not established as a direct oncogenic virus, its ability to activate these canonical tumor-promoting pathways provides a biologically plausible framework for

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understanding how COVID-19–associated inflammation may influence cancer progression and long-term disease risk [92,96,97].

6. Immune Evasion Mechanisms Shared by SARS-CoV-2 and Cancer

Effective immune evasion is a hallmark of both chronic viral infection and cancer, enabling persistence despite active host immune surveillance. SARS-CoV-2 infection induces multiple immunomodulatory programs that mirror canonical tumor immune escape strategies, including attenuation of antigen presentation, suppression of effector T cell function, and reprogramming of the local immune and metabolic microenvironment. Accumulating evidence indicates that viral infection and virus-induced inflammation can promote immune checkpoint upregulation while simultaneously fostering immunosuppressive and metabolically restrictive conditions that impair antitumor immunity.

6.1. Immune Checkpoint Upregulation and T Cell Inhibition

SARS-CoV-2 and cancer share strikingly convergent strategies for evading host immunity, most notably through the upregulation of inhibitory immune checkpoints that suppress T-cell function [100]. In both settings, these pathways blunt cytotoxic and helper T-cell responses, promote exhaustion-like phenotypes, and enable persistence of the pathogenic driver, whether a tumor or a virus [99,100]. This overlap reflects a deeper biological parallel. Chronic inflammatory signaling and hypoxic stress activate transcriptional programs that induce PD-1, PD-L1, TIM-3, LAG-3, and related inhibitory receptors, creating an immune landscape permissive to escape [98.101,102]. In SARS-CoV-2 infection, multiple mechanisms contribute to checkpoint upregulation [39,98]. The Wuhan strain and spike protein activate HIF-1 and TGF-β signaling in airway epithelial cells, inducing PD-L1, galectin-9, and Indoleamine 2,3-dioxygenase (IDO)1 and suppressing antiviral T-cell activity [100]. Clinical studies show that COVID-19 patients, especially those with severe disease, exhibit increased PD-1 expression and exhaustion-like transcriptional signatures in $CD8^+$ T cells [42]. In cancer patients with hematologic malignancies, SARS-CoV-2 infection further amplifies checkpoint expression, with elevated PD-1, TIM-3, and LAG-3 on T cells and impaired SARS-CoV-2–specific immunity, illustrating how pre-existing tumor-driven dysfunction synergizes with viral immune evasion [105].

Immune checkpoint upregulation is also a hallmark of cancer biology [103]. In breast cancer, PD-1, TIM-3, and LAG-3 are significantly elevated, accompanied by promoter demethylation and loss of repressive histone marks at checkpoint loci [103]. Breast cancer cells can directly induce PD-1, CTLA-4, TIM-3, and LAG-3 on $CD4^+$ T-cell subsets, and PD-1/PD-L1 blockade paradoxically increases TIM-3 and LAG-3 expression, reflecting compensatory inhibitory circuits [106]. Across solid tumors and hematologic cancers, co-expression of PD-1, TIM-3, and LAG-3 on intratumoral $CD8^+$ T cells correlates with disease progression, therapeutic resistance, and deep T-cell exhaustion [105.106]. These shared patterns converge on a common exhaustion program [102]. Chronic SARS-CoV-2 infection and cancer both generate T-cell populations characterized by PD-1high, PD-L1high, TIM-3, LAG-3, and TIGIT co-expression, reduced proliferation, impaired cytokine production, diminished cytotoxicity, and increased susceptibility to apoptosis [101,105]. Functionally, these exhausted states permit viral persistence in long-term COVID-19 and support tumor progression in cancer, underscoring the biological symmetry between viral and oncogenic immune escape [106,107]. These findings reveal that SARS-CoV-2 and cancer activate overlapping immune-evasion circuits centered on PD-1/PD-L1, TIM-3, and LAG-3, driven by hypoxia, inflammatory signaling, and chronic antigen exposure. This mechanistic convergence not only explains the profound T-cell dysfunction observed in severe COVID-19 and in cancer patients with SARS-CoV-2 infection but also highlights shared therapeutic vulnerabilities that may inform future immunomodulatory strategies [101].

6.2. Downregulation of Antigen Presentation Machinery, Establishing Immunosuppressive Microenvironment and Metabolic Reprogramming

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SARS-CoV-2 and cancer cells converge on several deeply conserved immune-evasion strategies, including suppression of antigen presentation, construction of immunosuppressive microenvironments, and metabolic rewiring that undermines effective $CD8^+$ and NK-cell immunity [108–110]. These shared mechanisms reveal a striking overlap between viral persistence programs and tumor immune escape, highlighting how chronic infection and malignancy exploit similar vulnerabilities in host defense [113].

Downregulation of antigen presentation is a central axis of immune evasion in both SARS-CoV-2 infection and cancer. SARS-CoV-2 accumulates mutations within Major histocompatibility complex (MHC)-I–restricted epitopes that reduce peptide–MHC binding and impair $CD8^+$ T-cell proliferation, IFN-γ production, and cytotoxicity [111,112]. Beyond epitope escape, the virus directly suppresses the antigen-processing machinery by inhibiting NOD-like receptor family CARD (caspase recruitment domain) containing (NLRC)5, the master transcriptional activator of MHC-I genes, thereby weakening presentation of viral peptides to $CD8^+$ T cells. Emerging variants, including Omicron sublineages, exhibit even stronger inhibition of surface MHC-I through coordinated actions of virus ORF7a, ORF6, and mutated E and M proteins, further reducing CTL-mediated killing and memory priming [115]. Cancer cells similarly downregulate MHC-I through genetic loss, epigenetic silencing, and oncogenic signaling pathways such as MAPK, EGFR, MYC, and SUMOylation, producing a parallel failure of antigen visibility that drives resistance to immunotherapy [116].

SARS-CoV-2 and tumors also sculpt profoundly immunosuppressive microenvironments enriched in dysfunctional myeloid and lymphoid populations [109,110]. Myeloid-derived suppressor cells (MDSCs) expand in chronic inflammation and malignancy, where they inhibit $CD8^+$ T cells and NK cells through arginase-1, iNOS, ROS/RNS, IDO, adenosine, and PD-L1, while simultaneously inducing regulatory T cells (Tregs) [111]. COVID-19 generates MDSC-like myeloid states that closely resemble tumor-associated MDSCs, marked by metabolic reprogramming and potent suppression of antiviral immunity [117]. These immunosuppressive niches also facilitate reactivation of latent herpesviruses such as EBV and CMV, events well-documented in cancer and severe viral infections, through impaired T-cell/NK N surveillance and elevated immunosuppressive cytokines [110,115,116].

Metabolic reprogramming represents a third shared mechanism linking SARS-CoV-2 infection to cancer-like immune escape. Viral proteins drive glycolytic shifts in lung epithelial cells and monocytes, increasing Pyruvate Kinase Isoenzyme Type M2 (PKM2) activity, Advanced Glycation End-Products (AGE)- Receptor for AGE System (RAGE) signaling [119], IL-1β and IL-6 production, senescence, and hypoxia [120]. SARS-CoV-2 inhibits mitochondrial oxidative phosphorylation, elevates mitochondrial reactive oxygen species (ROS), stabilizes HIF-1α, and diverts carbon flux into glycolysis and the pentose phosphate pathway, supporting viral replication while fueling mitohondrial (mt)DNA-driven inflammation [121]. These metabolic changes mirror the Warburg-like phenotype of cancer cells, characterized by aerobic glycolysis, lipid remodeling, oxidative stress, and ROS-induced DNA damage [120,121]. Tumor-infiltrating MDSCs exhibit similar metabolic signatures, enhanced glycolysis, fatty-acid oxidation, ER stress, and ROS/RNS production, that directly impair T-cell function and create a metabolically hostile, immunosuppressive niche [110,122].

All these mechanisms, MHC-I suppression, MDSC/Treg-dominated microenvironments, NK-cell dysfunction, and glycolysis-hypoxia-ROS metabolic rewiring, form a coherent immune-evasion architecture shared by SARS-CoV-2 and cancer [110]. This convergence explains the impaired $CD8^+$ responses observed in severe COVID-19 and provides a conceptual bridge linking viral immune escape to tumor-promoting biology [114].

7. Tissue-Specific Effects and Divergent Cancer Responses

SARS-CoV-2 exerts highly tissue-specific effects on cancer biology, accelerating malignant traits in some tumors while restraining others through differences in ACE2/Transmembrane serine protease (TMPRSS)2 expression, interferon signaling, and metabolic context [125]. Serwaa et al. demonstrated this divergence by infecting ACE2-expressing prostate (22RV1) and colorectal (DLD-1) cancer lines, revealing distinct changes in proliferation, apoptosis, migration, cytokine secretion,

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and cancer-marker expression, including Ki-67, BCL-2, vimentin, MMP9, and VEGF, after viral exposure [90]. Notably, despite low ACE2 expression in prostate tissue, 22RV1 cells remained highly infectable, suggesting contributions from alternative entry cofactors, viral mutations, and cell-cycle state [90]. In contrast, colorectal cancer cells, which naturally express higher ACE2/TMPRSS2 levels, exhibited stronger susceptibility and more pronounced pro-tumorigenic responses, consistent with clinical data showing worse COVID-19 outcomes in colorectal and thoracic cancers [124,125]. Prostate cancer presents a different landscape: TMPRSS2 is androgen-regulated, and androgen-deprivation therapy reduces TMPRSS2 expression and correlates with lower SARS-CoV-2 infection rates, potentially buffering against viral enhancement of tumor progression [126,127].

Mechanistically, ACE2/Renin–angiotensin–Aldosterone System (RAAS) signaling, interferon biology, and metabolic stress help explain why SARS-CoV-2 accelerates some cancers while suppressing others [130]. In ACE2-high gastrointestinal and lung tumors, viral-mediated ACE2 loss amplifies Ang II/AT1R signaling, driving proliferation, angiogenesis, hypoxia, ROS, and chronic inflammation, conditions favorable to carcinogenesis. Conversely, high baseline ACE2 expression in certain tumors correlates with reduced stemness, lower EMT, downregulated oncogenic pathways, and stronger antitumor immunity, suggesting a protective phenotype [69,128]. Interferon defects in some cancers permit unchecked viral replication, chronic inflammation, and oncogenic signaling, whereas IFN-high tumors predominantly induce the truncated dACE2 isoform, which does not bind spike and limits additional viral entry despite ACE2-labeled transcripts [129,130]. Metabolic context further shapes outcomes: ACE2 downregulation and Ang II excess promote ROS, DNA damage, and inflammatory cytokines in colorectal and thoracic tumors, while in other settings SARS-CoV-2 triggers apoptosis, cyclin-dependent kinase (CDK)4 downregulation, FasL upregulation, or immune activation that can restrain tumor growth, as reported in prostate models and in observations of tumor control following second infections [132]. This illustrates that SARS-CoV-2 does not exert a uniform effect on cancer but instead interacts with tissue-specific ACE2/TMPRSS2 patterns, RAAS and interferon signaling, and metabolic stress to either accelerate malignancy or potentially suppress growth [90]. This framework underscores the importance of tumor-intrinsic biology in shaping COVID–cancer interactions.

Moreover, recent work has demonstrated that SARS-CoV-2 infection can reactivate dormant metastatic cancer cells within the lung through inflammation-driven remodeling of the tissue microenvironment [133]. In murine models of breast cancer, SARS-CoV-2 rapidly disrupted the pro-dormancy phenotype of disseminated cancer cells, triggering proliferation within days and extensive metastatic outgrowth within weeks. This process was interleukin-6–dependent and accompanied by profound immune reprogramming, in which infection-impaired lung T cell activation and $CD4^+$ T cell–mediated suppression of $CD8^+$ cytotoxicity sustained metastatic burden, independent of direct viral infection of tumor cells [133]. Consistent with these experimental findings, analyses of cancer survivors from the UK Biobank and Flatiron Health databases revealed increased cancer-related mortality and lung metastasis following SARS-CoV-2 infection, underscoring the role of infection-induced, tissue-specific inflammation rather than uniform viral exposure in metastatic reactivation [133].

Given the central role of chronic immune dysregulation in shaping tumor-permissive environments, it is critical to distinguish infection-driven immune remodeling from vaccine-induced immune priming.

8. SARS-CoV-2 Vaccination as a Modifier of Cancer-Relevant Immune Pathways

SARS-CoV-2 vaccination provides a mechanistical contrast to natural infection with respect to immune activation, antigen persistence, and engagement of cancer-relevant signaling pathways. Whereas natural SARS-CoV-2 infection involves a replicating virus with prolonged antigen production and dissemination across epithelial, endothelial, and myeloid compartments, currently deployed COVID-19 vaccines rely on non-replicating platforms, including lipid-encapsulated mRNA (BNT162b2, mRNA-1273) and non-replicating adenoviral vectors (AZD1222, Ad26.COV2.S). These

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vaccines encode spike protein alone, lack replication capacity, and are cleared as mRNA degrades. Later, the transduced cells undergo apoptosis or immune-mediated elimination [132,133].

During infection, sustained viral RNA and protein persistence within tissues can maintain chronic activation of inflammatory and damage-sensing pathways, fostering immune dysregulation, fibrosis, and tumor-permissive microenvironmental remodeling [65,134–136]. Tissue tropism further distinguishes vaccination from infection. Productive infection embeds viral antigens directly within epithelial and stromal compartments, where activation of NF-κB, MAPK, and STAT3 signaling promotes cell survival, angiogenesis, epithelial–mesenchymal transition, and immune suppression [65,66,135]. In contrast, vaccine-derived spike expression is largely confined to professional antigen-presenting cells at the injection site and draining lymph nodes, with minimal dissemination to distant epithelial tissues and no generation of replicating virions [132,133]. Immunogenicity studies in patients with solid and hematologic malignancies demonstrate robust spike-specific immune priming after complete vaccination, without evidence of persistent antigenemia or systemic tissue exposure [132,133,137–140].

Innate immune activation induced by vaccination is also distinct in magnitude and kinetics. Severe SARS-CoV-2 infection as described above is characterized by prolonged elevation of IL-6, TNF-α, IL-1β, IFN-γ, GM-CSF, and chemokines, driven by viral replication, cell death, and engagement of innate sensing pathways including TRSrs and also cGAS–STING, resulting in sustained NF-κB and STAT3 signaling [18,65,89]. These inflammatory circuits support myeloid-derived suppressor cell expansion, pathological angiogenesis, and immunosuppressive signaling, hallmarks of oncogenic inflammation [65,66,132,135]. In contrast, mRNA- and adenoviral-vector vaccines induce acute, self-limited innate activation primarily within antigen-presenting cells, characterized by transient type I interferon and NF-κB signatures that resolve as antigen is cleared [132,133]. In clinical cohorts comprising thousands of vaccinated cancer patients, adverse effects are predominantly transient and localized, with no evidence of sustained systemic inflammation or cytokine dysregulation analogous to severe infection [132,137,139–141].

Recent mechanistic data further suggest that this transient innate activation can intersect with anti-tumor immunity in context-dependent ways. The study of Grippin et al. demonstrated that spike mRNA vaccination induces a brief type I interferon program that enhances dendritic-cell priming and promotes epitope spreading against tumor-associated antigens in preclinical models, while creating a signaling context permissive for synergy with immune checkpoint blockade [144]. Retrospective analyses within the same study linked recent mRNA vaccination to improved overall survival in subsets of patients with non-small-cell lung cancer and melanoma receiving immune checkpoint inhibitors, supporting the concept that vaccine-elicited innate activation can, under defined conditions, augment rather than impair antitumor immunity [144].

Adaptive immune responses elicited by vaccination also differ qualitatively from those arising during natural infection. Prolonged antigen exposure during infection, particularly in severe disease or immunocompromised hosts, is associated with lymphopenia and accumulation of virus-specific $CD4^+$ and $CD8^+$ T cells expressing inhibitory receptors such as PD-1 and TIM-3, reflecting functional exhaustion and impaired effector capacity [134,136,143]. Vaccination, by contrast, induces polyfunctional, Th1-skewed $CD4^+$ and $CD8^+$ T-cell responses cells that recognize multiple spike epitopes, including those conserved across variants [143–145]. In patients with solid tumors, vaccine-induced T-cell responses are frequently detectable even when humoral responses are attenuated by chemotherapy, and these cellular responses are augmented by booster doses [137,138,140,146]. Observational studies in patients receiving immune checkpoint inhibitors demonstrate preserved or enhanced vaccine-induced T-cell responses without increased immune-related adverse events, suggesting compatibility between vaccination and anti-tumor immunity [66,141,143]. Importantly, vaccine responsiveness does not strictly correlate with oncologic response: studies in long-term responders to PD-1/PD-L1 blockade demonstrate heterogeneous vaccine-induced humoral and cellular immunity despite sustained tumor control, indicating that antiviral and antitumor immune competence represent overlapping but non-identical immune states [149].

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At the level of intracellular signaling, natural SARS-CoV-2 infection can sustain activation of NF-κB, STAT3, and MAPK pathways through viral sensing, spike-mediated TLR2 activation, and autocrine cytokine loops in infected and bystander tissues, promoting survival signaling, immune evasion, and tissue remodeling [18,65,66,89]. Persistence of viral antigens raises concern for prolonged activation of these oncogenic pathways in susceptible epithelial compartments [65,66],135,136]. Although vaccination transiently engages overlapping pathways, activation is tightly regulated, restricted to immune cells, and rapidly resolves. Consistent with decades of vaccine experience, transient engagement of NF-κB and MAPK signaling in immune compartments is immunostimulatory rather than tumorigenic. Vaccination also activates NF-κB and MAPK pathways, but in a fundamentally different cellular and temporal context. Vaccine-induced signaling occurs primarily within APCs at the injection site and draining lymph nodes and is tightly coupled to antigen uptake, maturation, and migration. Transcriptomic profiling reveals early interferon and inflammatory signatures that resolve within days [132,133]. Here is no evidence of sustained NF-κB or STAT3 activation in epithelial or endothelial tissues analogous to that observed in severe infection.

Speculative hypotheses proposing potential long-term oncologic effects of repeated inflammatory exposures have been raised, often emphasizing non-genotoxic mechanisms such as chronic inflammation or altered immune surveillance. However, current evidence does not support vaccine-associated tumorigenesis, and such proposals remain hypothesis-generating rather than causal [150]. Consistent with mechanistic expectations, large post-marketing safety surveillance programs and population-based analyses have not identified an increased incidence of malignancy among individuals vaccinated against SARS-CoV-2 relative to background rates.

In patients with established cancer, SARS-CoV-2 vaccination confers clear clinical benefit. Prospective cohorts and meta-analyses report seroconversion rates of approximately 73–94% in patients with solid tumors and 60–65% in those with hematologic malignancies, with vaccine-induced cellular immune responses detected in roughly 60% of patients overall [132,133,137–141]. Although humoral immunity may be attenuated in individuals receiving B-cell–depleting therapies, vaccination substantially reduces severe COVID-19, hospitalization, and mortality in oncology populations [132,139–141]. Booster doses further enhance both humoral and cellular immunity with acceptable safety profiles [137,141,146].

Importantly, observational studies in patients receiving immune checkpoint inhibitors consistently demonstrate reduced COVID-19 severity following vaccination without an increased incidence of immune-related adverse events [66,141,143]. While some analyses suggest associations between vaccination timing and improved oncologic outcomes, these findings remain non-causal and should be interpreted cautiously. Collectively, available epidemiological data reinforce the conclusion that SARS-CoV-2 vaccination is safe in patients with cancer, does not increase cancer risk, and mitigates infection-related morbidity that could otherwise exacerbate immune dysregulation and disrupt cancer care.

Collectively, natural SARS-CoV-2 infection and vaccination occupy opposite ends of the spectrum with respect to cancer-relevant immune remodeling. Infection imposes prolonged antigen exposure, chronic inflammation, immune exhaustion, and sustained activation of oncogenic signaling pathways. In contrast, vaccination delivers a brief, compartmentalized antigen pulse that supports durable adaptive immunity without establishing persistent inflammatory niches. These mechanistic distinctions provide a critical framework for interpreting post-COVID immune alterations relevant to cancer biology and inform downstream clinical considerations.

9. Clinical Implications

Cancer patients with COVID-19 experience disproportionately severe outcomes, reflecting the combined effects of immune suppression, systemic inflammation, and treatment disruption [151]. Across multiple large cohorts, mortality rates range from 17–33%, substantially higher than in non-cancer populations, with hematologic malignancies, poor performance status, advanced age, comorbidities, and recent cytotoxic or monoclonal antibody therapy conferring additional risk

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[150,151]. Profound lymphopenia, affecting $CD4^+$, $CD8^+$, B cells, and NK cells, together with elevated IL-6, IL-8, CRP, and other inflammatory markers further predicts acute mortality and adverse trajectories [152,153]. Treatment interruptions are common, with up to 40% of patients experiencing delays of approximately three weeks, raising concerns about accelerated tumor progression [156].

Long-term surveillance data from cancer–COVID registries show that high inflammatory indices at diagnosis (CRP, LDH, D-dimer, NLR) not only predict acute severity but also correlate with persistent post-COVID sequelae, supporting the use of composite inflammatory scores such as the OnCovid Inflammatory Score for risk stratification [155]. Emerging hypotheses suggest that chronic low-grade inflammation, tissue injury, and potential viral persistence in long COVID may contribute to cancer progression, recurrence, or even *de novo* tumorigenesis, underscoring the need for vigilant follow-up in cancer survivors [157]. At the same time, the COVID–cancer interface reveals therapeutic opportunities. For example, p38/MAPK inhibition may mitigate Ang II–driven hyper-inflammation and organ injury; immune checkpoint inhibitors appear safe for many patients and may even confer protective immune reconstitution and targeted anti-inflammatory strategies, including IL-6 blockade and judicious steroid use, can be integrated with oncologic care to reduce COVID-19 morbidity without compromising cancer control [92]. Together, these findings highlight the dual challenge and opportunity posed by COVID-19 in oncology: heightened vulnerability requiring enhanced surveillance, and mechanistically informed interventions that may improve outcomes at the intersection of viral infection and cancer biology.

10. Conclusions and Future Directions

SARS-CoV-2 is not a classical oncogenic virus: it lacks dedicated viral oncogenes, does not typically establish long-term persistence, and differs fundamentally from canonical oncoviruses such as HPV, HBV, and EBV [63,136]. Nevertheless, mounting evidence shows that the virus perturbs multiple cancer-relevant pathways, creating conditions that may promote tumor initiation or progression in susceptible tissues [66]. Viral proteins can inhibit p53 and pRb, disrupt cell-cycle control, and rewire MAPK, NF-κB, JAK–STAT, RAAS, metabolic, and autophagy pathways, touching several hallmarks of cancer. COVID-19 and long-COVID states are characterized by chronic inflammation, oxidative stress, senescence, and fibrosis, particularly in the lung and gastrointestinal tract, all of which are recognized carcinogenic environments. Infection also induces immune exhaustion and impaired surveillance, including lymphopenia, dysfunctional $CD8^+$ and NK cells, and expansion of myeloid-derived suppressor cells, weakening antitumor immunity [158].

Persistent viral RNA or low-level infection, hypothesized in some individuals, may further sustain inflammatory and oncogenic signaling [71]. While current evidence does not support SARS-CoV-2 as a direct oncovirus, the convergence of chronic inflammation, immune exhaustion, tissue injury, and possible persistence justifies long-term vigilance [69]. Reviews consistently call for robust epidemiologic follow-up, mechanistic studies of persistent infection, and integrated biomarker strategies to monitor cancer risk in COVID-19 survivors [159]. The appropriate stance is neither premature reassurance nor alarm, but sustained scientific and clinical attention to the cancer-relevant consequences of SARS-CoV-2 [66,84].

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