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TP53 Dysregulation during SARS-CoV-2 Infection: Molecular Mechanisms, Cellular Consequences, and Therapeutic Perspectives (Article Review)

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ABSTRACT

Background: *Overview of COVID-19 pathogenesis and the central role of TP53 in maintaining genomic stability, DNA repair, apoptosis, immune regulation, and tumor suppression.* ***Objective:*** *To summarize current evidence regarding the interaction between SARS-CoV-2 infection and the TP53 signaling pathway and discuss potential cellular and clinical consequences.* ***Methods:*** *Literature search performed using PubMed, Scopus, Web of Science, and Google Scholar for studies published between 2020 and 2026.* ***Results:*** *Emerging evidence indicates that SARS-CoV-2 may suppress p53 activity through multiple molecular mechanisms involving MDM2-mediated degradation, modulation of antiviral signaling pathways, and interference with cellular stress responses. Reduced p53 activity may contribute to enhanced viral replication, impaired DNA repair, altered apoptosis, excessive inflammation, and immune dysregulation.* ***Conclusion:*** *Although current evidence supports transient dysregulation of TP53 signaling during SARS-CoV-2 infection, additional clinical and longitudinal studies are required to determine whether these alterations contribute to long-term pathological consequences, including carcinogenesis.*

Keywords: COVID-19; SARS-CoV-2; TP53; p53; MDM2; DNA Damage; Apoptosis; Cancer Biology; Long COVID.

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INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) since January 2020 has been one of the most consequential global public health challenges in the twenty-first century. More than 700 million individuals globally have been infected since its initial identification in late 2019 in Wuhan, China, and it has caused considerable mortality, socioeconomic disruption and long-term health consequences. Originally, COVID-19 was thought to be mainly a disease of the lungs but a growing body of evidence supports that SARS-CoV-2 interacts with host cellular, metabolic, immunological and genetic systems at multiple sites (Yamada & Takaoka 2023; Minkoff & tenOever 2023).

COVID-19 has a wide range in the severity of clinical manifestations, from asymptomatic infection and mild upper respiratory symptoms to severe pneumonia, acute respiratory distress syndrome (ARDS), multiorgan dysfunction, thromboembolic complications, and death.

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The idea that virulence or severity of disease is merely a function of viral replication has been to date hotly debated, with accumulating evidence supporting the notion that the host cellular response itself affects not only directly pathogenic processes but also contributes significantly to dysregulation of inflammatory signaling, oxidative stress, mitochondrial dysfunction and impaired antiviral immunity (Kapten et al., 2023; Yamada & Takaoka, 2023). These observations have triggered extensive explorations of the molecular mechanisms that govern interactions between hosts and viruses, as well as their ramifications on disease trajectory and chronic pathogenic sequela.

Viruses have developed highly sophisticated strategies to usurp host cellular machinery for their own ends to ensure survival and replication. Targeting components of key regulatory pathways in cell-cycle control, apoptosis, DNA repair, and immune surveillance is a hallmark of many DNA and RNA viruses. These interactions enable viruses to create a cellular context that is permissive for viral replication and antagonistic toward antiviral defense. Viral pathogens have evolved mechanisms, in recent evolutionary scales, to switch cellular pathways many of which play an important role through their accumulated association with human pathogenesis (Deng et al., 2022; Murakami et al., 2016).Among these frequently exploited cellular pathways is a central molecule in the interplay between viral infection and host response: p53, the tumor suppressor protein which plays an integral part in regulating cellular homeostasis and coordinating stress responses [18].

TP53 in 17p13 1, encodes p53 transcription factor that is commonly referred to as the "guardian of the genome," p53 is kept at low intracellular concentrations and tightly regulated under normal physiological conditions. On the other hand, p53 is activated in response to cellular stressors including DNA damage, oxidative injury, hypoxia, oncogene activation, or viral infection and then activates transcriptional programs regulating cell-cycle arrest, DNA repair processes senescence apoptosis autophagy immune responses. These mechanisms enable p53 to fulfil its pivotal functions in halting genomic instability and malignant transformation (Wang et al., 2023; Carlsen et al., 2023).

p53 plays critical roles in human health as TP53 is the most frequently mutated tumor suppressor gene in human cancers [10]. TP53 mutation/dysregulation of p53-linked pathways occurring in more than half of all cancers. In addition to its well-established role in tumor suppression, recent studies have elucidated an emergent functional role for p53 as a critical driver of both innate and adaptive immune responses. The protein is involved in antiviral defense through several mechanisms, including regulation of interferon signaling pathways, restriction of viral replication, and induction of apoptosis leading to the elimination of infected cells (Carlsen et al., 2023; Harford, 2023).

There is growing evidence that p53 has a pervasive antiviral role against different viral families including influenza viruses, hepatitis viruses, herpesviruses, human immunodeficiency virus (HIV), and coronaviruses. One major form of this approach is that viral pathogens regularly evolved methods to inhibit p53 activity, as sustained p53 activation can limit viral replication and contribute towards limiting the lifespan of infected cells. Therefore, a lot of viruses have acquired proteins to suppress p53 signalling, accelerate its degradation or inhibit its transcriptional activity (Harford, 2023; Wang et al., 2023).

Molecular studies uncovered that the TP53 pathway was manipulated similarly by SARS-CoV-2 to help the virus survive. Several experimental studies have shown that

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coronavirus infection could inhibit p53 activity via various mechanisms, including aberrations of ubiquitination pathways, dysregulation of cellular stress responses, and modulation of innate immune signaling. Multiple reports suggested that SARS-CoV-2 might facilitate degradation of p53 via Mouse Double Minute 2 (MDM2) an important upstream negative regulator of the stability and activity of p53 (Yao et al., 2024; Wang et al., 2023).

The MDM2–p53 regulatory axis is one of the most vital cellular checkpoints that maintain genomic integrity. Under physiological conditions, MDM2 binds p53 and facilitates its ubiquitination and proteasomal degradation resulting in low intracellular levels of p53. This interaction is disrupted by cellular stress, leading to accumulation and activation of p53. The pathway has been reported to be dysregulated in several diseases, including cancer, immune dysfunction, aging and viral pathogenesis. Emerging evidence indicates that SARS-CoV-2 may use host components of this regulatory network responsible for maintaining immune homeostasis to inhibit antiviral activities and facilitate viral replication (Yao et al. 2024).

A second key feature of SARS-CoV-2 pathogenesis relates to its capacity to evade recognition by the innate immune system. The rapid activation of pattern-recognition receptors (PRRs), type I interferons, inflammatory mediators and intracellular stress-response pathways are critical for effective antiviral immunity. However, SARS-CoV-2 has multiple immune-evasion strategies that will affect some of these protective mechanisms. Recent evidence emerges that p53 signaling pathway might be tightly integrated with the interferon response to infection resulting in suppression of p53 contributing to incompetent immune activation and prolonged viral persistence (Minkoff & tenOever 2023; Yamada & Takaoka 2023).

Beyond the acute infection phase, concerns about the long-term biological ramifications of SARS-CoV-2 infection have increasingly captured researchers' and public health officials' attention. Recent clinical reports in Long COVID patients do show evidence of persistent inflammation, oxidative stress and mitochondrial dysfunction, immune dysregulation, or changes in gene-expression profiles of various chronically affected tissues. Due to the fact that p53 functions as a master regulator of genome preservation and cellular responses to stress, TP53 signaling disruption is suggested to be an underlying mechanism in some of these chronic pathological changes (Kapten et al., 2023).

In addition, a number of investigators have questioned the potential oncogenic effects of perhaps persistent misregulation of tumor suppressor pathways in the aftermath SARS-CoV-2 (coronavirus responsible for COVID-19 infection). While there is no direct clinical evidence that COVID-19 causes cancer until now, mechanistic studies indicate transient downregulation of p53 activity, impaired DNA damage response and persistent inflammatory signalling may provide cellular microenvironments that promote genomic instability or enhance the potential for pathological transformation. Most of these observations have a speculative nature and need longitudinal validation before clear conclusions can be drawn (Wang et al, 2023).

The increase in literature regarding SARS-CoV-2 and host-cell signaling pathways has led to much interest in how human coronavirus infection is related with TP53 regulation. However, the existing observations are still dispersed in various disciplines like virology, molecular oncology, immunology and cellular biology. Therefore, a systematic review of available data is essential to illuminate the molecular basis for SARS-CoV-2/p53 signaling and to assess the functional relevance of such interactions on viral infection,

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regulation of immune response or disease outcomes over time.

Thus, the current review endeavors to critically evaluate available data surrounding SARS-CoV-2-mediated dysregulation of the TP53 pathway, summarize potential molecular mechanisms underlying p53 ,suppression in COVID-19 disease processes discuss cellular consequences of dysfunctional p53 signaling in diverse cell types during infection and immunity as well as address novel therapeutic options targeting activity in conjunction with the broad spectrum consequences on networks emanating from p53. Finally, this review outlines existing knowledge gaps in the field and future efforts needed to elucidate the biological consequences of SARS-CoV-2-mediated TP53 mutations/rearrangements in a .long-term perspective

2. Biology of TP53 and p53 Protein

2.1 Structure and Genomic Organization of TP53

Mutations in the tumor protein p53 (TP53) gene are found in more than 50% of human cancers, making TP53 one of the most investigated tumor suppressor genes in molecular biology and cancer research. Located on chromosome 17p13. TP53 is a multi-functional transcription factor that maintains the integrity of the genome and cellular homeostasis. P53 was acknowledged as a master regulator of cellular stress response from its discovery in 1979 because it can coordinate multiple biological processes, such as DNA repair, cell-cycle arrest, apoptosis and senescence, metabolism and autophagy, immune regulation (Wang et al., 2023).

The human TP53 gene is a 20 kb that consists of 11 exons and encodes a 393 amino acid protein. p53 protein is maintained in low levels under physiological conditions via ongoing degradation by ubiquitin-dependent proteasomal pathways. In contrast, a variety of cellular stress signals (e.g. DNA damage, oncogene activation, oxidative stress, hypoxia and nutrient deprivation, viral infection and inflammatory stimulation) lead to rapid stabilization and activation of p53 [5]. Once activated p53 acts largely as a transcription factor that modulates the expression of hundreds of stress-responsive target genes associated with adaptation to stress and cellular defence mechanisms (Huang et al., 2024).

The p53 protein is a structurally complex protein composed of functional domains that are highly conserved. It contains an N-terminal transactivation domain (TAD) that mediates interaction with transcriptional machinery and regulatory proteins. Next to this area you have a proline-rich domain related to apoptotic signalling and protein-protein interactions. The majority of the p53 functional landscape occurs at the central DNA-binding domain, where it binds to specific DNA response elements and exerts transcriptional regulation on target-gene expression. As you may know, most of the TP53 mutations identified in human cancers fall within this DNA-binding domain. The C-terminal region harbors an oligomerization domain for tetramerization and a regulatory domain implicated in post-translational modifications as well as stability control (Wang et al., 2023).

These domains are necessary for normal p53 function. Mutations that have a major impact on such functions as DNA binding, protein folding or tetramerization can severely impair the role of p53 in regulating cellular responses to stress, which enhances susceptibility for genomic instability and malignant transformation.

2.2 Physiological Functions of p53

2.2.1 p53 as the Guardian of the Genome

The title of p53 as the "guardian of the genome" highlights its essential function to protect cells from genomic instability. Post DNA damage, p53 is activated through a

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cascade of phosphorylation and acetylation events that inhibit its degradation and promote its transcriptional activity. Next, activated p53 triggers coordinated genetic programs that function to maintain genomic stability and inhibit the formation of damaged DNA (Wang et al., 2023).

Because accumulation of DNA lesions can result in mutagenesis leading to chromosomal abnormalities and/or oncogenic transformation, it is essential for cells to maintain the stability of their genomes [1]. Thus, p53 acts as a pivotal molecular switch in determining if damaged cells repair, enter a transient cell cycle arrest, become senescent or die by apoptosis.

2.2.2 Regulation of the Cell Cycle

Perhaps the most well established and earliest known function for p53 is its role in regulating cell-cycle progression. When DNA is damaged, p53 mediates the induction of cyclin-dependent kinase inhibitor 1A (CDKN1A), or more commonly known as a p21. This protein is the p16INK4a, a P21-like protein that inhibits CDK (cyclin-dependent kinase) complexes and prevents phosphorylation of retinoblastoma protein (Rb), arresting progression through the G1/S checkpoint as well. (Wang et al., 2023)

Cell-cycle arrest allows DNA repair pathways ample time to fix mutations, and halt replication at an appropriate time. Successful repair might allow the processing of cells to enter the cell cycle again. In contrast, continuous damage activates other p53-dependent pathways, promoting permanent growth arrest or programmed cell death.

Apart from G1/S regulation, p53 also plays a role in G2/M checkpoint control via transcriptional regulation of genes includingGADD45and14-3-3σ. Assembly of these mechanisms limits the transmission of genetic defects to daughter cells by preventing damaged DNA from entering mitosis.

2.2.3 DNA Damage Response and Repair

One of the most crucial protective functions of p53 is the DNA damage response (DDR). After genotoxic stress, p53 orchestrates overlapping repair pathways via transcriptional activation of genes in nucleotide excision repair, base excision repair, homologous recombination and non-homologous end joining.

When p53 is activated, it promotes the expression of the mediators involved in an repair process for DNA; these mediators include XPC, DDB2, GADD45 and p53R2. They are involved in DNA damage sensing, repair complex recruitment and genomic recovery. By each of these processes, p53 reduce the accumulation of mutations and protects from carcinogenesis (Huang et al., 2024).

Furthermore, recent studies have provided evidence that p53 not only participates in DNA repair but also mediates chronic inflammation caused by genomic instability. This newly proposed function emphasizes an also broader relevance of p53 in cellular and tissue homeostasis beyond its classical tumour-suppressive role.

2.2.4 Apoptosis and Programmed Cell Death

In the presence of DNA damage beyond repair capacity, p53 promotes a cellular transition from survival to apoptosis. This creates a barrier against the persistence of genetically unstable cells that cannot undergo malignant transformation.

The pro-apoptotic function of p53 is mediated in part through transcriptional activation of several BCL-2 family members, such as BAX, PUMA, NOXA and BID. These act in favor of mitochondrial outer membrane permeabilization, cytochrome c release, caspases activation and death (Wang et al.

Apart from transcription dependent mechanisms, p53 can directly bind with mitochondrial proteins to promote apoptosis

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without gene transcription. The two modes of action highlight p53 as a central regulatory node in promoting either cell survival or death during severe stress conditions.

2.2.5 Cellular Senescence and Aging

Abstract: Cellular senescence is characterised by permanent cell-cycle arrest, as well as associated metabolic and secretory changes. Senescence serves as a critical tumor-suppressive mechanism because it blocks the proliferation of incipient cancer cells.

Firstly, the p53 pathway is critical for initiating senescence and preventing malignant transformation under proper stimulation. In response to DNA damage, telomere shortening, oxidative stress or oncogenic signaling, p53 activation causes permanent cell cycle arrest and treats cells against malignant progression. On the other hand, sustained activation of senescence-associated pathways may also drive age-associated tissue failure (Huang et al., 2024).

Emerging evidence shows that this p53–MDM2 axis is finely tuned to regulate the antagonistic relationship between tumor suppression, tissue regeneration and aging/longevity. Thus, dysregulation of this pathway has relevance beyond cancer biology to age-associated disease and chronic inflammation conditions.

2.2.6 Metabolic Regulation

New evidence suggests that p53 serves as a central regulator of cellular metabolism. This transcriptional regulation of glycolytic, oxidative phosphorylation, fatty-acid oxidation and antioxidant defence systems by p53 is central to maintaining metabolic homeostasis during both physiological and stress conditions.

Mutant p53 inhibits excessive glycolysis and promotes mitochondrial respiration, thus reversing the so-called Warburg effect of metabolic alteration, hailed as a hallmark of cancer. Additionally, regulation of oxidative stress and cellular senescence is modulated directly by p53 through regulation of antioxidant genes, controlling reactive oxygen species (ROS) levels to limit oxidative damage and maintain cellular integrity.

The perception of p53 as a metabolic regulator has not only broadened its classical tumor-suppressor functions but has also allowed for novel investigations into its role(s) in response to virulent pathogens, chronic inflammation and oncogenic stress associated with aging.

2.3 The p53–MDM2 Regulatory Axis

2.3.1 MDM2 as the Principal Negative Regulator of p53

In the case of normal physiology, p53 activity is under the strict control of Mouse Double Minute 2 (MDM2), an E3 ubiquitin ligase and primary negative regulator of p53. MDM2 directly binds to the N-terminal transactivation domain of p53, leading to ubiquitination, nuclear export and proteasomal degradation of p53 (Huang et al., 2024).

This forms a classical negative feedback loop. Transcription of MDM2 is induced by activated p53, while overexpressed MDM2 then in turn inhibits a p53 function and normalizes protein abundance. This autoregulatory circuit enables cells to achieve the proper level of p53 activity while avoiding excessive or persistently elevated p53 activation that would compromise tissue function.

2.3.2 Stress-Induced Disruption of the MDM2–p53 Interaction

Following exposure to DNA damage or other stress signals, several kinases such as ATM, ATR and CHK2 phosphorylate both p53 and MDM2. These changes are thought to reduce the affinity of protein interactions between MDM2 and p53, and inhibit breast cancer MDM2-dependent degradation.

This leads to accumulation of p53 in the nucleus, followed by further post-translational modifications that culminate in activation of transcription of hundreds of stress-response

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genes. Such a mechanism serves as an essential molecular switch governing cellular adaptation to environmental or intracellular stresses.

2.3.3 Clinical and Therapeutic Significance

The MDM2–p53 pathway is frequently dysregulated in a large number of human cancers and has emerged as an attractive drug development target. A number of small-molecule MDM2 inhibitors have been developed as a means to rescue p53 function through disruption of the interaction between p53 and MDM2. Such agents are now being tested in the context of Oncology and could serve a therapeutic role in diseases caused by defected p53 signaling (Huang et al., 2024).

Prior research into coronavirus biology had noted that components of the MDM2–p53 regulatory network may be used by SARS-CoV-2 to inhibit infection-fighting responses and promote viral replication. This finding offers a mechanistic rationale for investigating TP53 dysregulation in the context of COVID- and underscores the need for further 19 investigation of p53 biology during viral .pathogenesis

3. SARS-CoV-2 and Host Cell Manipulation

3.1 Viral Structure and Genome Organization

As is commonly known, the new human coronavirus (SARS-CoV-2) is classified as an enveloped positive-sense single-stranded RNA virus of the Betacoronavirus genus. The ~30 kb genome encodes two large open reading frames (ORF1a and ORF1ab), which generate the nonstructural proteins needed for viral replication, along with four main structural proteins: spike (S), envelope (E), membrane (M) and nucleocapsid (N) 3.

The spike protein is the main mediator of host-cell entry. S1 has a receptor-binding domain that interacts with angiotensin-converting enzyme 2 (ACE2), and S2 then allows for membrane fusion, allowing the virus to infect (Yang & Rao, 2021).

Besides structural and replication proteins, SARS-CoV-2 encodes accessory proteins that can fine-tune host signalling pathways that inhibit antiviral responses as well as enhance immune evasion. These functions aid in viral replication and may counteract cellular stress-response pathways, including those orchestrated by p53 (Minkoff & tenOever, 2023).

3.2 Viral Entry Mechanisms

3.2.1 ACE2-Mediated Viral Attachment

In SARS-CoV-2 infection, the initial step is binding of the spike protein to ACE2, a transmembrane carboxypeptidase expressed in various tissues including respiratory tract, gastrointestinal epithelium, cardiovascular tissues, kidneys and central nervous system [6]. The widespread distribution of ACE2 goes a long way towards explaining the multisystem manifestations associated with COVID-19 (Minkoff & tenOever, 2023).

Within S1, the receptor-binding domain has high-affinity interaction with ACE2 and mediates conformational changes that to prime the virus for membrane fusion. Expression analyses showed extremely high levels of ACE2 in nasal goblet and ciliated epithelial cells, indicative that the upper respiratory tract represents a major portal of viral entry and early replication (Sungnak et al., 2020).

Most importantly, ACE2 engagement is not a passive attachment event. Receptor binding triggers several intracellular signaling cascades linked with oxidative stress, inflammatory responses, and changes in the cellular metabolism. These early host responses overlap with DNA damage response pathways and cellular stress adaptation, both of which are tightly regulated by p53. Therefore, the first step of viral entry facilitated by ACE2 subsequently initiates a chain reaction of cellular events that may culminate in modulation of TP53 signaling.

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3.2.2 TMPRSS2-Mediated Spike Protein Priming

After receptor attachment, proteolytic activation of the spike protein occurs by host proteases, most prominently transmembrane serine protease 2 (TMPRSS2) [15]. The spike protein is cleaved at the S1/S2 and S2′ sites, enabling subsequent fusion of viral and cellular membranes upon release of the viral genome into cytoplasm (Minkoff & tenOever, 2023).

Entry through TMPRSS2-dependent pathways has been widely accepted as one of the most effective methods for SARS-CoV-2 infection in airway epithelial cells. While in certain contexts other endosomal entry pathways and cathepsins may also play a role in infection, TMPRSS2 clearly represents a key determinant of viral infectivity and tissue tropism. SARS-CoV-2's dependence on host proteases reflects the proclivity of the virus toward viral entry through manipulation of cellular machineries and emphasizes its susceptibility to host-directed therapeutic approaches (Yang & Rao, 2021).

Viral entry triggers cellular stress responses that activate signaling cascades regulating apoptosis, oxidative stress response and innate immune sensing pathways are intimately linked to TP53 biology. The interaction of these pathways with p53 may acquire even more importance as infection advances and replicates actively.

3.3 Viral Replication Cycle

The SARS-CoV-2 RNA genome is released into the cytoplasm as soon as it enters the host cell and acts directly as messenger RNA to direct translation of the ORF1a and ORF1ab polyproteins. These polyproteins are cleaved by viral proteases into non-structural proteins (NSPs), which then aggregate to form the replication–transcription complex (RTC) that is responsible for viral RNA synthesis (Yang & Rao, 2021).

The RTC produces negative-sense RNA intermediates that can then be used as templates for replication of new genomic and subgenomic RNAs. AT MAM, we propose that structural and accessory proteins are synthesised in the endoplasmic reticulum (ER) and chaperoned to ERGIC before virion assembly. Subsequently, this newly formed virions are released by way of exocytosis (Yang & Rao 2021; Minkoff & tenOever 2023).

Viral replication exerts enormous metabolic stress on virus-infected cells and leads to widespread cellular reprogramming, including changes in mitochondrial activity, energy metabolism, lipid synthesis, protein production. While these alterations facilitate the environment for viral spread, they also induce oxidative stress and cell death. Thus, SARS-CoV-2 replication is tightly coupled with cellular stress-response pathways (Fig. 1), many of which are regulated by p53 [9], underscoring the importance of TP53 signaling in shaping host responses to infection.

3.4 Mechanisms of Immune Evasion

The ability to overcome the host antiviral defenses is crucial for successful viral replication. SARS-CoV-2 has developed similar strategies that disrupt innate immune recognition and inhibit antiviral signal transduction pathways (Minkoff & tenOever, 2023).

Some of the characteristic features of COVID-19 pathogenesis are the late induction of type I and type III interferons in early responses against SARS-CoV-2 infection. Many viral proteins target critical components of pathogen recognition receptor pathways (e.g. RIG-I, MDA5, MAVS, TBK1 and STAT signaling pathways) and antagonize either the production or action of interferons. Instead, this suppression decreases the overall level of antiviral immunity and allows replicating virus to replicate effectively until adaptive immune responses are sufficient in duration and

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strength (Sievers et al. 2024 Minkoff & ten Oever 2023).

Besides antagonism of interferon responses, SARS-CoV-2 also exploits additional mechanisms to reduce the detection of viral RNA by host sensors. Viral RNA processing pathways prevent the cell from accumulating these immune-stimulating RNA species to dampen the amount of pathogenic signaling through innate immune mechanisms. In addition, many viral proteins also affect networks involving antigen autonomy and demarcation of aggravated phenotypes by hindering attractions networks to indicative signals, which have been shown to be dysregulated in severe COVID-19 (Minkoff & tenOever, 2023).

p53 has also recently emerged as an important effector of antiviral immunity, which is particularly relevant to the present review. Previous studies have shown that p53 can facilitate interferon responses, promote apoptosis of infected cells and restrict viral replication. Hence, viral tactics that inhibit interferon signalling could thereby compromise p53-mediated antiviral responses. The functional convergence aligns the mechanistic basis for how SARS-CoV-2 may harness TP53 signaling underpinning a wider strategy to evade host immunity and establish productive infection.

4. Molecular Mechanisms of TP53 Suppression during SARS-CoV-2 Infection

4.1 Evidence from Transcriptomic Studies

Transcriptomic characterization of SARS-CoV-2–infected cells and human samples from patients indicates deep changes in the host cell transcriptome, notably affecting the innate immunity gene networks, apoptosis regulation, stress responses and other pathways [6]. Importantly, multiple studies showed downregulation of p53-mediated apoptosis and DNA damage response genes and activation of inflammatory and survival signaling pathways (Blanco-Melo et al., 2020; Wang et al., 2023).

In addition, single-cell RNA sequencing also reinforced that COVID-19 is associated with an aberrant transcriptional profile in severe cases characterized by down-regulated antiviral programs and up-regulated inflammatory signatures. The authors found TP53 to be a hub gene on this network, which suggests that its functional suppression may underlie inhibited cellular antiviral defenses (Wyler et al., 2021).

The integrative flow of evidence from these transcriptomic signatures suggests that SARS-CoV-2 infection liberates an immunity modulatory mechanism which acts though p53-dependent genomic supervision to yield a progenitor virus permissive transcriptional state.

4.2 Viral Proteins Affecting p53 Signaling

SARS-CoV-2 Messages SARS-CoV-2, like all viruses, encodes multiple non-structural and accessory proteins capable of interacting with important host regulatory pathways. Among them, papain-like protease (PLpro, part of NSP3) that is supposed to sabotage host ubiquitin and interferon signaling systems.

Experimental data on coronaviruses that are related to SARS-CoV has shown that PLpro functions as a virus-induced stabilizer of host E3 ubiquitin ligases like RCHY1 can downregulate p53 and suppress the antiviral responses (Ma-Lauer et al., 2016) While experimental validation in SARS-CoV-2 has been scarce, there is structural conservation that supports the hypothesis of a similar mechanism in COVID-19 pathogenesis (Gordon et al., 2020).

SARS-CoV-2 proteins also have been reported to broadly interact with host factors involved in apoptosis, RNA processing and protein degradation—many of which converge within p53 regulatory networks.

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4.3 MDM2-Mediated Degradation of p53

The MDM2–p53 axis is the main regulatory pathway that regulates intracellular p53 levels. MDM2 acts as an E3 ubiquitin ligase that promotes the proteasomal degradation of p53 and is essential for keeping low basal level of p53 under physiological levels.

3a, 5c), then stress signaling and inflammatory pathways could further activate MDM2 during viral infection that positively regulated p53 degradation. SummaryRecent studies indicate that viral manipulation of the MDM2–p53 axis is a general strategy used by different viruses to inhibit animal defences and allow intracellular persistence. Disruption of this pathway could lead to impaired p53-dependent apoptosis, interferon signaling and genomic surveillance mechanisms. (Huang et al., 2024) This decreases the stability of p53, which inhibits essential functions downsteam: apoptosis, DNA repair and activation of antiviral genes (Yao et al., 2024)).

MDM2-mediated suppression is a key mechanism through which SARS-CoV-2 may indirectly promote viral persistence since p53 plays a central role in limiting viral replication.

4.4 RCHY1 and Ubiquitination Pathways

Besides MDM2, another key p53-stabilizing E3 ubiquitin ligase is RCHY1 (or Pirh2) [8]. Before, studies have shown that SARS-CoV viral papain-like protease can stabilize RCHY1, increasing the ubiquitination and degradation of p53 (Ma-Lauer et al. 2016).

Since SARS-CoV-2 displays extensive structural homology to SARS-CoV it is therefore likely the similar regulatory interactions occur during COVID-19 infection. Furthermore, elevated activity of RCHY1 may facilitate the inhibition of both p53-dependent apoptosis as well as immune responses and thus aid in viral replication [30].

This reduntant viral strategy of dual ubiquitin-mediated regulation (MDM2 and RCHY1) in targeting p53 stability. Figure 1 summarizes the proposed mechanisms by which SARS-CoV-2 inhibits p53 activity.

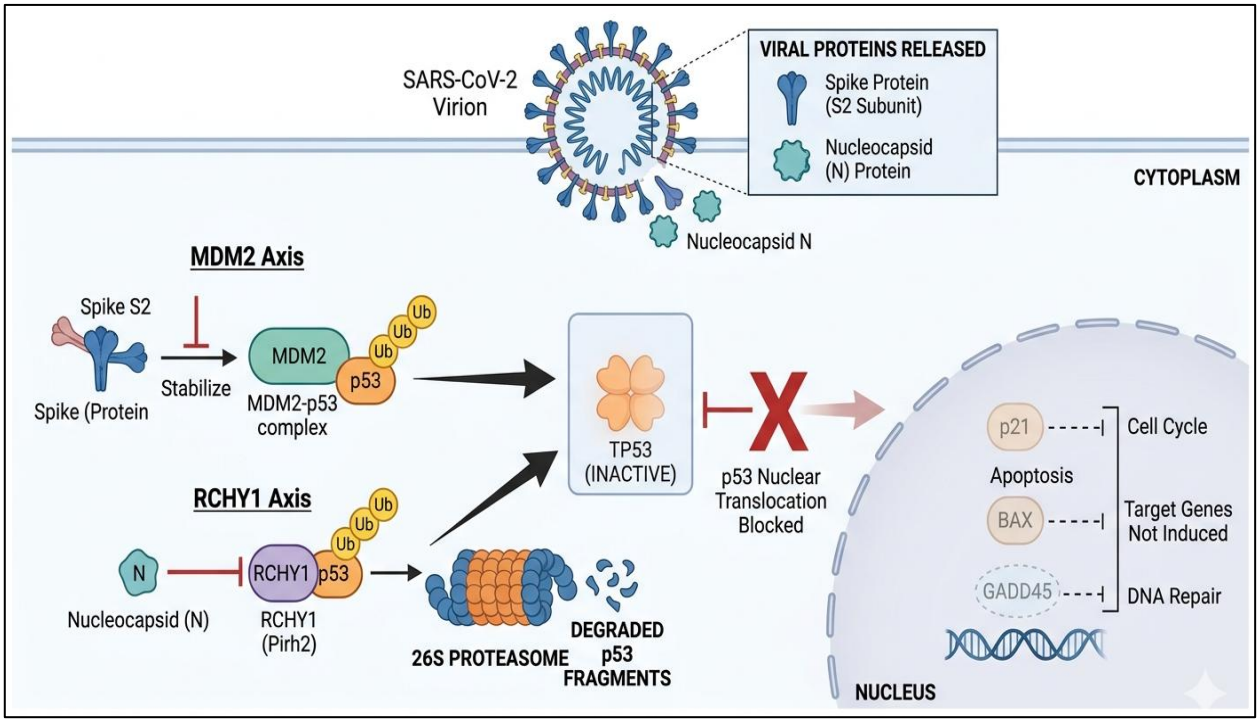

Figure 1. Proposed mechanisms by which SARS-COV-2 suppresses p53 activity through MDM2, RCHY1, and related pathways.

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4.5 Interaction with Interferon Signaling

The first line of defense against viral infections is provided by type I and III interferons. Perhaps p53 contributes to antiviral immunity, both by increasing transcription of interferon-stimulated genes and driving apoptosis in infected cells.

By contrast, SARS-CoV-2 inhibits interferon production and downstream JAK–STAT signaling and thus impairs antiviral responses (Minkoff & tenOever, 2023). Aty though this indirect suppression is an important part of direct interference with p53 activation by the virus, signaling through interferon does contribute to stabilization and function of support for p53.

On the contrary, inhibition of p53 activity attenuates interferon responses and establishes a negative feedback cycle that promotes virus replication (Park & Iwasaki, 2020).

4.6 Crosstalk with NF-κB Pathways

NF-κB serves as a key mediator of inflammation and is particularly upregulated in association with SARS-CoV-2 infection. Transient NF-κB activation enhances antiviral defense, but sustained NF-κB activation leads to chronic inflammation and cytokine dysregulation.

Complex antagonistic interactions between NF-κB and p53 pathways Continuous activation of NF-κB can inhibit p53-dependent apoptosis and, thus, allows for cell survival in the presence of genotoxic stress. The dysregulation of these pathways may prolong survival of infected cells promoting viral replication and inflammatory damage (Blanco-Melo et al., 2020; Wang et al., 2023).

Therefore, NF-κB hyperactivation in COVID-19 may be responsible for the functional inhibition of p53.

4.7 Oxidative Stress and Mitochondrial Dysfunction

SARS-CoV-2 infection induces significant oxidative stress through mitochondrial dysfunction, inflammatory signaling, and immune cell activation. Elevated reactive oxygen species (ROS) levels lead to DNA damage and metabolic reprogramming.

Under normal conditions, p53 acts as a key regulator of oxidative stress by inducing antioxidant genes and maintaining mitochondrial integrity. However, excessive ROS production can disrupt p53 regulatory balance and promote functional suppression or dysregulation (Codo et al., 2020).

Mitochondrial damage further impairs innate immune signaling and enhances viral replication Recent studies have also linked mitochondrial dysfunction to persistent metabolic abnormalities observed in post-acute COVID-19 syndrome. Impaired mitochondrial homeostasis may sustain oxidative stress, inflammatory signaling, and cellular senescence long after viral clearance (Bohmwald et al., 2024). Given that mitochondria are central to both apoptosis and p53 activation, mitochondrial dysfunction is a critical mechanism linking SARS-CoV-2 infection to disruption of the TP53 pathway (Saleh et al., 2020). A summary of key studies investigating the effects of SARS-CoV-2 on TP53 signaling is presented in **Table 1.**

Table 1. Summary of Studies Investigating SARS-CoV-2 Effects on TP53 Signaling.

Study	Year	Study Type	Main Findings	Relevance to TP53
Blanco-Melo et al.	2020	Transcriptomics	Dysregulated host response and impaired interferon signaling	Indirect suppression of p53-mediated antiviral pathways
Gordon et al.	2020	Proteomics	SARS-CoV-2 protein-host interaction map	Identified interactions affecting cellular regulatory pathways

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Study	Year	Study Type	Main Findings	Relevance to TP53
Wyler et al.	2021	Transcriptomics	Altered expression of stress-response genes	Evidence of TP53 pathway perturbation
Wang et al.	2023	Review	Comprehensive analysis of p53–coronavirus interactions	Central evidence linking SARS-CoV-2 and p53
Minkoff & tenOever	2023	Review	Immune evasion mechanisms	Interferon-p53 interaction
Harford	2023	Review	Antiviral role of p53	Therapeutic implications
Yao et al.	2024	Review	MDM2-mediated p53 regulation	Potential therapeutic target

5. Cellular Consequences of p53 Dysregulation during SARS-CoV-2 Infection

5.1 Impaired DNA Damage Response

Tumor suppressor protein p53 is central to orchestrating DNA damage sensing, activation of cell-cycle checkpoints, and DNA repair pathways that are critical for genome integrity. Under physiological conditions, exposure to genotoxic stress leads to activation of p53, which in turn results in the transcriptional up-regulation of several genes encoding proteins that play a role in nucleotide excision repair, base excision repair, homologous recombination and cell-cycle arrest. As a result, repression of TP53 signaling in SARS-CoV-2 infection likely has severe outcomes on the cellular DDR (Wang et al., 2023).

There is growing evidence that infection with SARS-CoV-2 results in elevated oxidative stress, replication stress and DNA damage signalling. Chronic induction of ROS may lead to DNA strand breaks and genomic instability, but concurrent inhibition of p53 decreases the ability of infected cells to trigger appropriate repair responses (Saleh et al., 2020). In addition, p53-dependent checkpoint pathways may be deregulated to allow survival of cells with damaged DNA and provide an avenue for genomic instability and chronic cellular abnormalities [37].

AbstractRecent transcriptomic analyses have revealed dysregulation of many DNA-damage-response (DDR)-related genes in cells infected with SARS-CoV-2, implicating engagement and/or maladaptation of cellular genome surveillance mechanisms in the pathophysiology of COVID-19 (Wyler et al., 2021). While the long-term consequences are still being explored, disruption of DNA repair pathways is a biologically plausible consequence of p53 inhibition in infection.

5.2 Defective Apoptosis

Apoptosis is an essential antiviral response as it controls viral spread through the elimination of infected cells following, or during a specific phase of the viral replication cycle. The tumor suppressor protein p53, known as the central regulator of programmed cell death, induces the transcription of several pro-apoptotic genes such as BAX, PUMA, NOXA and BID to trigger mitochondrial-mediated apoptosis upon serious cellular damage [13] (figure 3).

Thus, suppression of p53 signalling may inhibit the capacity of infected cells to trigger apoptosis in a time-dependent manner. Coronaviruses of course have a very different approach, as delaying host-cell death is advantageous to them: the longer a cell can survive whilst virally replicating and assembling new virions, the better! Other experimental studies have shown that the coronavirus-mediated degradation of p53 decreases activation of apoptotic pathways, consequently providing a cellular environment conducive for viral persistence (Ma-Lauer et al., 2016).

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Additionally, impaired apoptosis could lead to phenotypic accumulation of dysfunctional cells with abnormalities in mitochondria, metabolism and inflammation. Thus, p53 suppression not only promotes viral replication but may also worsen tissue damage in COVID-19.

5.3 Enhanced Viral Survival and Replication

In addition to apoptosis, p53 has direct structures during viral infection by adjusting innate immune signaling and interferon response therefore serving an important role in cellular stress adaptation. Since a functioning p53 pathway poses a major roadblock to viral replication, multiple viruses have evolved strategies to dampen the activity of this well-characterized tumor suppressor (Wang et al., 2023).

Specifically, in the context of a coronavirus infection, p53 activation can lead to cell-cycle arrest and depletion of metabolic resources necessary for viral replication, and stimulate antiviral gene expression. Consequently, targeted degradation or functional inactivation of p53 by viruses may confer a selective replicative advantage. Research on the interplay with viruses such as coronaviruses has also linked reduced p53 activity to improved viral multiplication rates and increase viral fitness (Ma-Lauer et al., 2016; Wang et al., 2023).

The suppression of p53-dependent restriction mechanisms might also support prolonged intracellular persistence of viral RNA and proteins. This might be particularly true in severe COVID-19, characterized by prolonged viral replication and impaired viral clearance.

5.4 Immune Dysregulation and Enhanced Inflammation

Apart from its tumor-suppressive functions, p53 appears to be holding an important role in the regulation of both antiviral immunity and inflammatory responses. P53 is a transcription factor that modulates the expression of numerous genes regulating interferon signaling, cytokine production and immune-cell homeostasis in order to optimize viral control while restricting aberrant inflammation (Park & Iwasaki, 2020). Such suppression of TP53 signaling when SARS-CoV-2 infects potentially undermines interferon-mediated antiviral defenses and hinders immune responses, thus enhancing viral persistence and dissemination (Minkoff & tenOever, 2023).

In parallel, lower p53 activity may erode its capability to repress inflammatory signaling by losing inhibitory effects on NF-κB pathways. This may lead to the increased synthesis of pro-inflammatory mediators including IL-6 and TNF-α, thereby exacerbating tissue damage, endothelial dysfunction, severe COVID-19 outcomes (Blanco-Melo et al., 2020; Wang et al., 2023).

In addition, chronic inflammation can additionally inhibit p53 function by oxidative stress and other cellular damage, which leads to a vicious cycle of immune dysregulation and inflammation [57] Long COVID is another condition characterized by chronic immune activation, with many inflammatory mediators as well as changed immune-cell phenotypes and dysregulated cytokine signaling remaining detectable months after acute infection (Ceglarek & Boyman, 2024). Figure 2Major Downstream Cellular Consequences of p53 Suppression During SARS-CoV-2 Infection.

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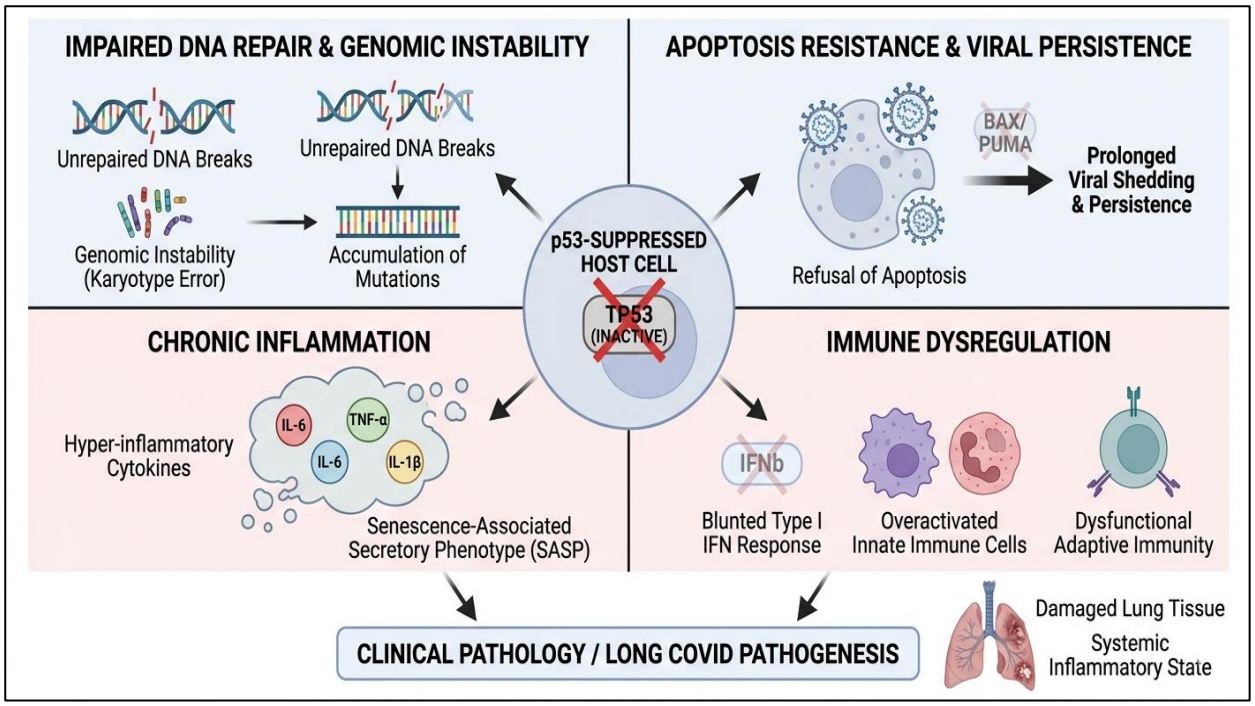

Figure 2. Potential downstream consequences of p53 suppression including impaired DNA repair, apoptosis resistance, immune dysregulation, and chronic inflammation.

5.5 Cellular Senescence

Cellular senescence is a state of permanent cell-cycle arrest associated with extensive changes in metabolism and secretion. While senescence appears as a protective mechanism preventing the proliferation of damaged cells, its excessive accumulation promotes tissue dysfunction, chronic inflammation and age-related diseases (Yao et al., 2024).

There is a very complex relationship between p53 and senescence. In normal condition, p53 participates to coordinate the proper cellular senescence response to DNA damage or cellular stress. On the other hand, chronic viral infection, continued oxidative stress and abnormal p53 signaling may encourage non-canonical senescence-associated phenotypes (Saleh et al., 2020).

Accumulating evidence suggests that SARS-CoV-2 infection may induce premature cellular senescence by mitochondrial dysfunction, inflammatory cytokine signaling and oxidative stress. Senescent cells are characterized by their senescence-associated secretory phenotype (SASP); proliferative signals can induce senescence-like cellular states in response to SARS-CoV-2 infection via DNA damage responses, oxidative stress pathways, mitochondrial dysfunction and p53/p21 signaling. The build-up of senescent cells may play a role in chronic inflammation, defective tissue regeneration and long-term post-viral sequelae (Bohmwald et al., 2024).

These included pro-inflammatory cytokines, growth factors and proteases that lead to chronic tissue inflammation and immune dysregulation (Blanco-Melo et al., 2020).

Since p53 is a well-established mediator of senescence programs, we speculate that its dysregulation during COVID-19 does not only worsen severity of acute disease but may also underlie long-lasting post-viral complications. These observations have led to great interest in the targeting of senescence-associated pathways as possible therapeutic approaches for reducing COVID-19-related tissue damage.

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6. Potential Long-Term Consequences of TP53 Dysregulation Following SARS-CoV-2 Infection

6.1 Genomic Instability and Potential Oncogenic Consequences

The p53 protein plays a central role in maintaining genomic stability through regulation of DNA repair, cell-cycle checkpoints, and apoptosis. Consequently, SARS-CoV-2-induced disruption of TP53 signaling may impair cellular responses to DNA damage and reduce the ability of cells to eliminate genetically compromised populations (Wang et al., 2023).

Several studies have shown that SARS-CoV-2 infection promotes oxidative stress, mitochondrial dysfunction, and activation of DNA damage pathways. Excessive generation of reactive oxygen species (ROS) can induce DNA strand breaks, chromosomal abnormalities, and replication stress, all of which contribute to genomic instability (Saleh et al., 2020). Under normal conditions, p53-mediated mechanisms limit the propagation of damaged genomes; however, suppression of p53 activity may compromise these protective responses.

These observations have raised questions regarding the possible long-term implications of SARS-CoV-2 infection for cancer-related processes. Although SARS-CoV-2 is not classified as an oncogenic virus and there is currently no evidence that COVID-19 directly causes cancer, several biological features associated with infection—including chronic inflammation, oxidative stress, DNA damage accumulation, immune dysregulation, and impaired tumor suppressor activity—are recognized contributors to carcinogenesis (Wang et al., 2023; Yao et al., 2024).

Nevertheless, available evidence remains largely mechanistic and insufficient to establish a causal relationship between SARS-CoV-2 infection and cancer development. Therefore, potential oncogenic consequences should be regarded as a theoretical possibility requiring long-term epidemiological and molecular investigation rather than a demonstrated clinical outcome.

6.2 Persistent Inflammation

Abstract Persistent inflammation is one of the most consistent biological features observed post SARS-CoV-2 infection. Studies have shown that once acute infection resolves there is extended activation of components implicated in inflammation, complement pathways and immune signalling networks for months (Altmann et al., 2023; Ceglarek & Boyman, 2024).

Under physiological conditions, p53 opposes NF–κB signaling to promote resolution of inflammation and limit excessive cytokine production. Thus, sustained inhibition of p53 can lead to persistent stimulation of inflammatory signaling pathways and establishment and maintenance of a pro-inflammatory microenvironment (Wang et al., 2023).

Chronic inflammation has been recognised as an important contributor to endothelial dysfunction, tissue remodelling, fibrosis, metabolic derangements and immune dysregulation. In conjunction, this could cumulatively predispose a proportion of patients who recovered from SARS-CoV-2 infection to the well-known phenotypes of long COVID (Bohmwald et al., 2024). These findings suggest p53 dysfunction could be one of many possible explanations bridging the gap between acute viral infection and chronic inflammatory sequelae.

6.3 Long COVID Syndrome

Long COVID—and more formally the Post-Acute Sequelae of SARS-CoV-2 Infection, or PASC—is a condition that involves symptoms persisting for weeks or months after recovery from infection in the acute phase. Clinical manifestations encompass fatigue, cognitive impairment ("brain fog"), dyspnea, dysautonomia,

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musculoskeletal pain, sleep disturbances and cardiovascular abnormalities (Davis et al., 2023; Al-Aly et al., 2024).

Long COVID pathophysiology is likely multifactorial, incompletely understood. Possible mechanisms of Long COVID development include viral persistence, immune dysregulation, chronic inflammation, endothelial dysfunction, autoimmunity, mitochondrial impairment and persistent tissue damage (Altmann et al., 2023; Bakerly et al., 2024).

Many of these mechanisms share common aspects with biological processes under the control of p53. In the nuclear compartment, p53 is critical not only for cell cycle regulation but also as an important player involved in mitochondrial homeostasis and control of oxidative stress, apoptosis, cellular senescence and also immune modulation [8]. As a result, persistent TP53 dysregulation during or following acute infection may help explain some of the molecular defects found in Long COVID (Wang et al., 2023).

However, direct evidence linking dysfunction of p53 to particular symptoms of Long COVID is still scarce. Future studies that encompass transcriptomics, proteomics and systems biology could identify whether persistent TP53 dysregulation predisposes to particular Long COVID phenotypes and disease trajectories (Bakerly et al., 2024). Deeper mechanistic studies will be needed to elucidate the degree of this connection.

6.4 Current Evidence and Limitations

While there is growing evidence for the idea that SARS-CoV-2 can interact with p53 pathways, some important limitations should be acknowledged.

First, not all of the mechanistic p53 degradation evidence is based on direct experimental verification during SARS-CoV-2 infection (Ma-Lauer et al., 2016; Muñoz-Fontela et al., 2020), but instead, derived from studies with either SARS-CoV or other coronaviruses. Although coronavirus proteins are actually structured similarly, extrapolation must be undertaken carefully.

Second, most observations related to TP53 dysregulation are based on analyses from transcriptomic, proteomic and bioinformatic studies. While these approaches provide important information on host-pathogen interaction, they do not always demonstrate direct causation.

Third, Long COVID is presumed to be a heterogenous syndrome driven by multiple overlapping biological mechanisms. Therefore, p53 dysregulation cannot be the only explanation for all long-term effects, and only one potential mechanism among many (Al-Aly et al. 2024; Altmann et al. 2023).

Finally, the impact of TP53 alterations associated with SARS-CoV-2 in the long-term clinical presentation is still unknown. Identification of these molecular mechanisms has laid the foundation for future experiments aimed at generating in vivo data on whether transient p53 suppression during infection leads to long-term biological consequences that influence genomic stability, immune regulation, aging-related processes and cancer susceptibility.

In summary, there is emerging evidence in favor of the hypothesis that SARS-CoV-2 might hijack p53-driven cell-defense mechanisms and resultantly give rise to long-term pathological pathways. However, significant knowledge gaps persist which underscores the importance of expanded experimental and translational work to infill between basic science advances and clinical implementation.

7. Therapeutic Perspectives

The increasing awareness of the ability of SARS-CoV-2 to hijack TP53-related pathways kindled interest in p53 function restoration and/or targeting the downstream effects of p53 dysregulation. Because p53 is a hub of antiviral defense, apoptosis, immune

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regulation and maintenance of genomic integrity, therapeutic modulation of this pathway may not only bear the potential for simultaneous inhibition of viral replication but also amelioration of unwanted pathological host responses. Yet p53 controls many critical cellular functions therefore disrupting these pathways must be done judiciously to mitigate potential toxicities or unnecessary activation of apoptotic pathways (Wang et al., 2023).

7.1 MDM2 Inhibitors

Molecular restoration of p53 activity is one of the most widely studied strategy and the MDM2 antagonist is a main representative, as MDM2 is an E3 ubiquitin ligase that regulates p53 degradation. MDM2 directly and negatively regulate the activity of p53, constituting a homeostatic feedback system at a physiological state. However, overactivity of MDM2 can lead to pathological inhibition of p53 (Yao et al., 2024).

Various small-molecule MDM2 inhibitors, such as Nutlin-3, idasanutlin, milademetan and navtemadlin (KRT-232), have been focused on anti-tumor use. Small molecules that interfere with the MDM2–p53 interaction, leading to stabilization and activation of wild-type p53. Restoration of p53 function increases apoptosis, cell-cycle arrest, DNA repair and antiviral gene expression (Konopleva et al., 2020).

During coronavirus infection, preservation of p53 function may enhance the clearance of infected cells while also enhancing innate immunity response limiting viral replication as showed by experimental evidence (Wang et al., 2023). While clinical trials specifically evaluating MDM2 inhibitors in COVID-19 are pending, these compounds appear as suitable candidates for host-directed therapeutic approaches.

However, systemic p53 activation may have detrimental effects including hematologic toxicity and overshooting in normal tissue injury [136], thus emphasizing the necessity for dose optimization together with careful patient selection.

7.2 p53 Activators

In addition to the selectivity for MDM2 inhibition, another attractive strategy is to directly activate p53. Many drug compounds have been developed to improve p53 transcription activity, stabilize the protein structure of dysfunctional p53 molecules or restore function to mutated p53 molecules.

Small molecules including APR-246 (eprenetapopt), first developed to reactivate mutant p53 in neoplastic cells, have been shown to exert wider actions, modulating both cellular stress responses and apoptosis pathways (Lehmann et al, 2012). Moreover, compounds that target post-translational modifications of p53 could augment its antiviral function due to increases in protein stability and transcriptional competence.

Accumulating evidence indicates that p53 activation contributes to its antiviral potential by directly regulating many interferon-stimulated genes and antiviral restriction factors. Thus, p53 activation can exert two benefits: it may inhibit viral replication while enhancing immune control of infection (Harford, 2023).

Nevertheless, as overactivity of p53 may induce apoptosis in uninfected tissues, the therapeutic strategy should focus on regulated and site-specific activation instead of ubiquitous stimulation.

7.3 Host-Directed Antiviral Therapies

Traditional antiviral therapies primarily target viral proteins and replication machinery. In contrast, host-directed therapies aim to modulate cellular pathways exploited by viruses, thereby reducing the likelihood of antiviral resistance and potentially providing broader antiviral activity.

The p53 signaling network represents an attractive target for host-directed intervention because many viruses, including coronaviruses, have evolved mechanisms to

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suppress p53 function. Restoration of host antiviral pathways may enhance viral clearance while preserving immune homeostasis (Wang et al., 2023).

Potential host-directed strategies include modulation of:

- p53 signaling pathways,
- interferon responses,
- ubiquitin–proteasome systems,
- oxidative stress pathways,
- Mitochondrial function.

This therapeutic paradigm may be particularly valuable against emerging viral variants because it targets conserved host mechanisms rather than rapidly mutating viral proteins (Minkoff & tenOever, 2023).

Nonetheless, host-directed therapies require careful evaluation because interference with fundamental cellular processes may result in unintended consequences affecting immune regulation, tissue repair, and metabolic homeostasis. Potential therapeutic strategies targeting the p53 pathway and their proposed mechanisms are summarized in **Table 2.**

Table 2. Potential Therapeutic Agents Targeting the p53 Pathway During COVID-19.

Therapeutic Strategy	Representative Agents	Mechanism of Action	Potential Benefit
MDM2 inhibitors	Nutlin-3, Idasanutlin, Milademetan	Prevent p53 degradation	Restore antiviral responses
p53 activators	APR-246 (Eprenetapopt)	Enhance p53 activity	Promote apoptosis of infected cells
Interferon-based therapy	IFN-α, IFN-β	Enhance antiviral signaling	Indirect activation of p53 pathways
Antioxidants	N-acetylcysteine (NAC)	Reduce oxidative stress	Preserve p53 function
Host-directed therapies	Multi-target approaches	Modulate host antiviral pathways	Reduce viral replication and inflammation

8. Limitations of Current Evidence

Although there is growing interest in the association of SARS-CoV-2 infection and TP53 dysregulation, various caveats should be taken into account while interpreting current observations. First, a large fraction of existing data is derived from in vitro studies, transcriptomic analyses and computational models rather than clinical studies or assessments. Although these methods give mechanistic insights into host–virus interactions, they may fail to faithfully recapitulate in vivo biology.

Some hypothesized mechanisms of p53 suppression come from studies with SARS-CoV-1 and other coronaviruses. While SARS-CoV-1 and SARS-CoV-2 share key biological features, predictions would need to be tested corroboratively in suitable experimental models before they can be directly extrapolated.

Third, although TP53 signaling during the acute, recovery and post-acute phases of COVID-19 is suggested to be potentially important in prospective longitudinal clinical studies, such data are limited. Therefore, the duration and clinical relevance of p53 dysregulation following SARS-CoV-2 infection has not yet been elucidated.

SIGNIFICANCE Chronic inflammation, oxidative stress, genomic instability and impaired tumor suppressor activity are

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established mechanisms that contribute to carcinogenesis however there is currently no direct clinical evidence that SARS-CoV-2 infection promotes cancer through TP53-associated pathways. Consequently, the suggested oncogenic potential is speculative at this stage and awaiting confirmation in studies to characterize long-term epidemiological and mechanistic effects.

All of these restrictions emphasize the need for thorough in vivo research, larger longitudinal cohorts, and extended follow-up studies to define the biological relevance and clinical impact of TP53 dysregulation in COVID-19.

9. Research Gaps and Future Directions

In spite of considerable advancements in our comprehension of SHRs after SARS-CoV-2 infection, substantial gaps in knowledge persist. Emerging evidence suggest that p53 functions as a critical anti-viral defence system and SARS-CoV-2 virus may target and sabotage p53-mediated cellular functions. Nevertheless, despite these important advances many mechanistic and clinical questions remain unanswered. Filling these gaps will be critical for assessing the ultimate biological and clinical relevance of TP53 dysregulation in COVID-19 and for informing rational treatment approaches (Wang et al.

9.1 Current Limitations of Available Evidence

While interest in the intersection between SARS-CoV-2 infection and p53 signaling is increasing, the current literature has several critical limitations. To begin with, no long-term longitudinal clinical study has been carried out assessing whether p53-related changes returned to normal levels after recovery from COVID-19. The data currently available mostly stem from cross-sectional or short-term studies, thus characterizing the timing, reversibility, and clinical relevance of TP53 pathway de-regulation remains challenging (Al-Aly et al., 2024). Thus it is unclear whether the inhibition of p53 observed during acute infection results in long-term effects or simply constitutes a transient adaptive mechanism that resolves following viral clearance (Altmann et al., 2023).

Second, much of the mechanistic evidence is based on in vitro experiments, computational analyses or transcriptomic studies rather than direct in vivo investigation. While these are valid approaches that have proposed potential mechanisms such as MDM2 activation, ubiquitin-mediated p53 degradation, loss of interferon signaling, and mitochondrial dysfunction; the physiological significance in living organisms has not yet been validated (Wang et al., 2023). Thus, future studies are needed on prospective clinical cohorts in addition to animal models, organoid systems and multi-tissue analyses to confirm these mechanisms and determine when SARS-CoV-2 induces p53 changes in tissues. These types of studies are necessary to determine causality and importantly the lasting effects on health resulting from p53 dysregulation in patients surviving COVID-19.

9.2 Future Research Priorities

Two important areas for future research may help to clarify the long-term effects of SARS-CoV-2-mediated p53 dysregulation. The establishment and validation of reliable biomarkers that reflect p53 pathway activity may enhance risk stratification as well as therapeutic monitoring, and enable timely identification of individuals at risk for Long COVID or other persistent complications. Potential biomarkers that will be reviewed include TP53 gene expression profiles, levels of circulating p53 protein, MDM2 activity, indicators of DNA damage responses and oxidative stress and signatures for cellular senescence and interferon-responsive transcription. Technologies in multi-omics are evolving, such as transcriptomics, proteomics, metabolomics or single-cell sequencing which

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may help identifying molecular signatures associated with TP53 dysfunction and support the construction of personalized predictive models utilizing artificial intelligence-based methods (Davis et al., 2023).

The second research trend is long-term cancer surveillance of COVID-19 survivors Current evidence does not back the classification of SARS-CoV-2 as being oncogenic, however several biological processes triggered or potentiated by COVID-19 such as chronic inflammation, oxidative stress, genomic damage, immune dysregulation and potential suppression of tumor suppressor pathways are known drivers of cancer. Larger population-based longitudinal studies are therefore warranted to assess the incidence of cancer, cancer-specific mortality, tissue-specific risks and genomic instability biomarkers involved in COVID-19 survivors. These studies should control for bias, particularly those due to healthcare disruptions, deferred cancer screening programs and changing lifestyle habits or preexisting co-morbidities as SARS-CoV-2 exposure may or may not have long-term meaningful impacts on p53 alterations and risk for developing future cancers (Wang et al., 2023; Yao et al., 2024). In summary This review summarizes the current knowledge gaps and priorities in future research involving TP53 dysregulation in coronavirus disease-19 (COVID-19) **Table 3.**

Table 3. Knowledge Gaps and Future Research Priorities.

Research Area	Current Limitation	Future Priority
TP53 expression in COVID-19	Limited longitudinal data	Long-term cohort studies
MDM2–p53 interactions	Predominantly in vitro evidence	In vivo validation
RCHY1-mediated degradation	Evidence largely derived from SARS-CoV	Direct SARS-CoV-2 studies
Long COVID mechanisms	Multifactorial and incompletely understood	Molecular characterization
Cancer risk after COVID-19	Insufficient epidemiological evidence	Long-term surveillance studies
Biomarker development	Lack of validated TP53 biomarkers	Multi-omics approaches
Therapeutic targeting of p53	Limited clinical trials	Precision medicine strategies

10. Clinical Relevance

As a key regulator of antiviral immunity, inflammation, DNA repair and cellular homeostasis, understanding TP53 dysregulation during SARS-CoV-2 infection is clinically relevant. Accumulating evidence indicates that inhibition of p53 activity may be implicated in many pathophysiological features of COVID-19. Deficient p53 function can hindering antiviral responses and may promote viral replication leading to increased disease severity (Ceglarek & Boyman, 2024; Altmann et al., 2023).

In addition, the disruption of p53-mediated control of inflammatory pathways may underlie the overwhelming cytokine production and immune dysregulation seen in severe COVID-19.

Although p53 dysregulation is well described during the acute phase of an infection, this alteration may also have clinical relevance following infection. Sustained mutations in cellular stress responses, immune

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regulation, and tissue repair responses have been suggested to play a role in the development of post-acute sequelae of COVID-19 (Long COVID) (Al-Aly et al, 2024; Davis et al., 2023). The direct causal links need to be elucidated, but chronic alterations in the p53 signaling pathway may increase susceptibility to persistence of chronic inflammation and cellular senescence and delayed recovery in certain patients.

It is also potentially a target for therapy as TP53 signalling is targeted in therapeutic approaches. Approaches to reactivate or retain p53 activity may be beneficial, as they can restrict viral replication, reduce inflammation-mediated host damage and promote cellular recovery after infection. Multiple p53-modulatory drugs, specifically MDM2-p53 inhibitors, have promising effects in preclinical studies and should be further ,.evaluated (Harford et al., 2023; Wang et al Therefore, improved understanding of .(2023 the regulation of TP53 during SARS-CoV-2 infection could advance knowledge regarding COVID-19 pathogenesis while aiding in the discovery of new therapeutic strategies and prognostic biomarkers for acute and chronic .disease outcomes

11. CONCLUSION

The tumor suppressor protein p53, which is encoded by the TP53 gene, is critical to cellular homeostasis due to its role in regulating DNA repair, cell-cycle progression and geographic apoptosis (Gasco et al., 2002; Vousden and Prives, 2009) along with fabricating oxidative stress response mechanisms (Hoh and Harris, 2014), as well as immune surveillance (Wang et al., 2023) and antiviral defence (Kepp et al., 2021). Apart from its well-established role in tumor suppression, p53 is an important effector of host defense against coincident viral infections. Growing evidences indicate that SARS-CoV-2 is capable of sabotaging p53-regulated pathways through several direct and indirect mechanisms, most likely supporting its replication and immune evasion.

Recent studies show that SARS-CoV-2 promotes p53 degradation via ubiquitin-dependent pathways, modifies the MDM2–p53 regulatory axis, inhibits interferon signaling and induces oxidative stress as well as inflammation and mitochondrial dysfunction. These changes potentially modulate antiviral responses, lead to reduced apoptosis of infected cells and affect DNA damage repair. Therefore, the p53 dysregulation may promote not only acute COVID-19 pathogenesis but also long-lasting disturbances of cellular and immune homeostasis owing to alternative consequences of aberrant proliferative signalling.

Additional interest has been stirred about a potential role of p53 dysfunction in Long COVID pathophysiology. Multiple biological processes that are commonly described in post-COVID conditions, such as chronic inflammation, oxidative stress, mitochondrial dysfunctionities, cellular senescence and immune dysregulation are infiltrated pathways typically under the control of p53. While still indirect, sustained disruption of TP53-associated signaling networks during infection may drive some long-term molecular effects observed in COVID-19 survivors.

In addition, the potential contribution of SARS-CoV-2-induced p53 dysregulation to cancer-related processes is another area currently under study. SARS-CoV-2 is not an oncogenic virus, and clinical evidence does not establish that COVID-19 causes cancer as a disease, but chronic inflammation, oxidative stress, genomic instability and inhibition of tumor suppressor pathways are established mediators of carcinogenesis. Long-term epidemiologic studies are needed to ascertain whether stable molecular changes after infection affect the risk of subsequent malignancy.

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In addition, the increasing evidence regarding SARS-CoV-2–p53 interactions has revealed potential therapeutic targets. Strategies to restore p53 activity or inhibit upstream regulatory pathways may boost virally-induced responses but dampen injury-related inflammation. Considering the pleiotropic physiological roles of p53, such strategies would certainly need to be executed with caution.

Conclusion In short, p53 is an important molecular bridge between antiviral immunity, inflammation, genomic stability, and survival. More knowledge gaps exist, but further understanding of the SARS-CoV-2–TP53 axis may provide novel insights into COVID-19 pathogenesis, identify novel therapeutic targets, and clarify long-term health consequences related to SARS-CoV-2 infection.

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