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Review

The p53/Mdm2 Pathway in Hepatocellular Carcinoma: From Molecular Pathogenesis to Targeted Therapies

Keara Kirkness [1,2] and Derek A. Mann [1,2,*]

[1] Newcastle Fibrosis Research Group, Biosciences Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne NE2 4HH, UK; keara.kirkness@newcastle.ac.uk
[2] The Newcastle University Centre for Cancer, Newcastle University, Newcastle upon Tyne NE2 4HH, UK
* Correspondence: derek.mann@newcastle.ac.uk

Abstract

Hepatocellular carcinoma (HCC) is the most common type of liver cancer, and accounts for over 800,000 deaths worldwide, making it a major global health concern. Unfortunately, despite major advances in systemic treatments, such as the introduction of atezolizumab and bevacizumab, patient objective response rates fall below 30%. HCC most commonly develops against a background of chronic liver disease and cirrhosis, although single gene mutations can also drive HCC development, progression, and metastasis. Around 25% of HCC patient tumours carry mutations in *TP53*, the gene encoding the tumour-suppressor protein p53. p53 is a central regulator of genomic stability, cell-cycle arrest, apoptosis, senescence, and metabolic homeostasis, and its dysfunction is a frequent event in hepatocarcinogenesis. Accumulating evidence highlights the critical role of p53 in liver fibrosis, inflammation, and shaping of the HCC tumour microenvironment (TME). This review summarizes the role of p53 and its negative regulators Mdm2 and MdmX in HCC development and progression, with an emphasis on how p53 shapes the TME in favour of tumour progression. We also evaluate current and emerging p53-targeted therapeutic strategies, including Mdm2/MdmX inhibitors, mutant p53 reactivators, and rational combinations with immunotherapies. Finally, we discuss major challenges in translating p53-based therapies to the clinic, such as tumour heterogeneity, underlying liver dysfunction, and the development of therapeutic resistance. A deeper understanding of p53 biology in chronic liver disease may unlock new avenues for effective HCC prevention and treatment.

Keywords: hepatocellular carcinoma; p53; mdm2; liver tumour microenvironment; immunotherapy; inflammation; fibrosis; senescence

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1. Introduction

The stress response programme, regulated by the p53 protein, is a diverse and complex process that controls gene expression and multiple signalling pathways involved in functions such as cell cycle arrest, DNA repair and apoptosis. Through these mechanisms, p53 helps prevent genomic instability and malignant transformation.

Discovered in 1979 [1,2], the 393-amino acid residue p53 protein was originally thought to be a viral-associated oncogene. Studies investigating viral aetiology using Simian Virus 40 (SV40)-transformed mouse cell lines identified a 53 kilodalton cellular protein that was antigenic, bound to the viral large T antigen, and was highly expressed in transformed cells. However, the protein was too large to be coded from the SV40 genome, so it was concluded

that it must be of cellular origin. Subsequent studies demonstrated that overproduction of p53 in rat embryonic fibroblasts correlated with tumorigenesis [3,4]. In 1989 however, it was revealed that these earlier SV40 experiments involved mutant forms of p53. In contrast, wild-type (wt) p53 suppressed transformation and inhibited cellular proliferation. As a result, p53 was reclassified as a tumour-suppressor protein [5–7]. By the 1990s, the role of p53 in DNA damage response was more extensively studied, with p53 being importantly termed the so-called "guardian of the genome" [8] because of its central role in controlling a variety of processes such as DNA repair, cell cycle arrest and apoptosis.

Under normal physiological conditions, p53 protein levels are low, and primarily located in the cytoplasm. However, when cells encounter stress signals such as hypoxia, oxidative stress and DNA damage, p53 forms tetramers that become phosphorylated, activated and stabilised prior to their translocation into the nucleus to regulate target gene transcription [9]. Activation of p53 allows cells to temporarily suspend their cell cycle and repair damaged DNA. In circumstances where DNA damage is severe or irreparable, p53 instead promotes the transcription of genes also involved in cellular senescence (*CDKN1A*, *CDKN2A*) and apoptosis (*BAX*, *BCL2*, *BBC3*, *PMAIP1*).

It is well known that p53 is a master regulator of cell fates, with over 3000 target genes involved in classical pathways [10,11], such as cell cycle arrest, apoptosis and senescence. More recently, it has been unveiled that p53 is a major contributor to additional key cellular processes including metabolism, autophagy, ferroptosis, metastasis and immunity (Figure 1) [12–16]. Given the central role of chronic inflammation, fibrosis and regenerative proliferation in hepatocarcinogenesis, dysregulation of p53 signalling has particularly important consequences in the liver. Loss of p53 activity not only permits survival of genomically unstable hepatocytes, but also reshapes the hepatic tumour microenvironment through effects on immune surveillance, stromal activation and metabolic regulation.

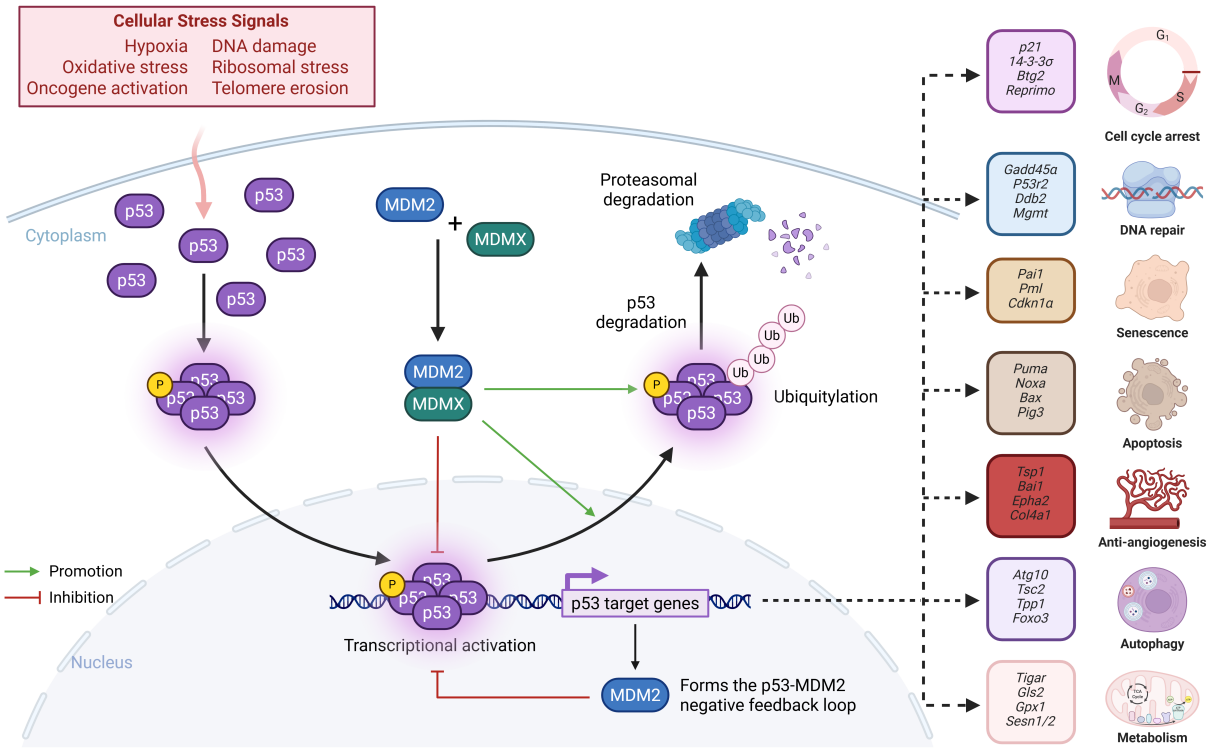

Figure 1. Role of p53 and regulation by Mdm2 and MdmX. The tumour-suppressor protein p53 is located in the cytoplasm under normal physiological conditions, but when the cell undergoes stress p53 is phosphorylated and forms tetramers with itself. Activated p53 tetramers are translocated to the nucleus where they bind to target genes to activate several pathways such as cell cycle arrest,

DNA repair, senescence, apoptosis, anti-angiogenesis, autophagy and metabolism. p53 transcriptional activity can be regulated by both Mdm2 and/or MdmX. Mdm2 regulates p53 activity by binding to p53 via the TAD domain, therefore preventing p53 from binding to target genes. The Mdm2/MdmX complex also promotes the nuclear export of p53 into the cytoplasm, where Mdm2 acts as an E3 ubiquitin ligase to tag phosphorylated p53 for proteasomal degradation. Target gene transcription by p53 also results in the production of Mdm2, forming a p53/Mdm2 negative feedback loop. Abbreviations: Mdm2, Mouse Double Minute 2 homolog; MdmX, Mouse Double Minute X homolog; TAD, trans-activating domain. Figure created with BioRender.com.

1.1. DNA Repair, Cell Cycle Arrest and Apoptosis

p53 has a vital role in reducing genomic instability and protecting the genome by controlling both DNA repair and apoptosis. As part of the DNA damage response (DDR), genomic stresses trigger the activation of specific enzymatic cascades that initiate cell cycle arrest and DNA repair mechanisms such as base excision repair, nucleotide excision repair, mismatch repair and homologous recombination, many of which involve p53 [17]. The DDR activates the stress sensor kinases ataxia-telangiectasia mutated (ATM) or ATM- and Rad3-Related (ATR), which subsequentially phosphorylates and activates p53 to trigger downstream signalling pathways [18]. One mechanism by which p53 halts the cell cycle is through stimulation of *CDKN1A* gene transcription, leading to expression of the cyclin-dependent kinase (CDK) inhibitor p21. This results in suppression of CDK activity, specifically CDK1, CDK2, CDK4 and CDK6 [19], and phosphorylation of the Retinoblastoma protein (Rb): subsequently, hypophosphorylated Rb binds to E2F transcription factors halting the G1/S transition. Cell cycle arrest at the G2/M phase is also regulated by p53 through induction of *SFN* and *GADD45A*, which encode proteins that inhibit formation of the mitotic cyclin B1/Cdc2 complex [20]. In cases where DNA damage is extreme, activation of p53 can directly initiate transcription of pro-apoptotic genes, as well as bind and inhibit anti-apoptotic proteins such as Bcl-2, Bcl-xL and Mcl-1, further initiating the cell death effectors BAX and BAK [21].

1.2. Senescence

Depending on the extent of DNA damage, the activation of ATM/ATK and p53 can trigger the upregulation of p21 and E2F1, resulting in the state of cell cycle arrest known as cellular replicative senescence. The activation of E2F1 within the cell cycle is paradoxical, as E2F1 normally promotes proliferation by activating S phase genes, inducing DNA repair machinery and promoting cell cycle progression. However, when E2F1 is overexpressed, it can trigger permanent growth arrest through transcription of CDKN2A, stabilisation of p53 and further activation of p21 [22,23]. Within this process, the p53/p21/E2F1 axis promotes cell cycle arrest cells at the G1 phase, while repressing mitosis-specific genes such as cyclin A, cyclin B and Cdc2/CDK1 [24]. These events place cells in a state in which they are no longer able to re-enter the cell cycle. Cellular senescence can be initiated through multiple physiological and metabolic pathways, and is therefore considered a heterogenous phenotype.

Senescent cells are characterised by both phenotypic and molecular markers that are context dependent. However, most phenotypes of senescence include distinct morphological changes, such as senescence-associated β-galactosidase activity, chromatin remodelling, metabolic reprogramming and the production of the senescence-associated secretory phenotype (SASP), which can alter the immune landscape and promote tumorigenesis. The SASP includes a wide variety of soluble factors such as cytokines (IL-6 and IL-8), growth factors (such as transforming growth factor-β (TGF-β)) and matrix-modifying enzymes that reinforce and promote senescence spread in the microenvironment [25,26].

The SASP can also exacerbate inflammatory and pro-lipogenic mechanisms to drive steatotic liver disease [27–29], the latter a condition in which HCC can develop in the absence of cirrhosis [30]. Senescent liver cells, together with the SASP, can promote steatosis primarily through mitochondrial and metabolic dysfunction. These senescent hepatocytes exhibit glucose and lipid metabolic disturbances which result in increased reactive oxygen species (ROS) production, reduced fatty acid oxidation, and increased insulin resistance, thereby promoting lipid accumulation [31–33].

1.3. Cancer

One of the principal functions of p53 is to prevent genomic instability and suppress tumorigenesis. However, more than 50% of malignancies are associated with mutations in the *TP53* gene, resulting in dysregulation of downstream p53 signalling pathways and progression towards malignancy [34]. These mutations often fail to initiate apoptotic pathways, thereby enabling uncontrolled malignant cell proliferation. Consequently, mutated forms of p53 represent an important therapeutic target in cancer, as strategies aimed at restoring p53 function or targeting mutant p53 may suppress tumour progression and potentially resensitise malignant cells to existing cancer therapies [35].

2. Structure, Function and Regulation of p53

The p53 protein comprises six functional domains, including the transactivation domains 1 and 2 (TAD1 and TAD2) which are responsible for p53 transcriptional activity, with TAD2 also providing the binding site for the regulatory protein mouse double minute 2 (Mdm2) [36] (Figure 2). The remaining domains include a proline-rich domain (PRD), a DNA binding domain (DBD) for DNA sequence specific binding, a tetramerization domain (TET) and a C-terminal regulatory domain (CTD).

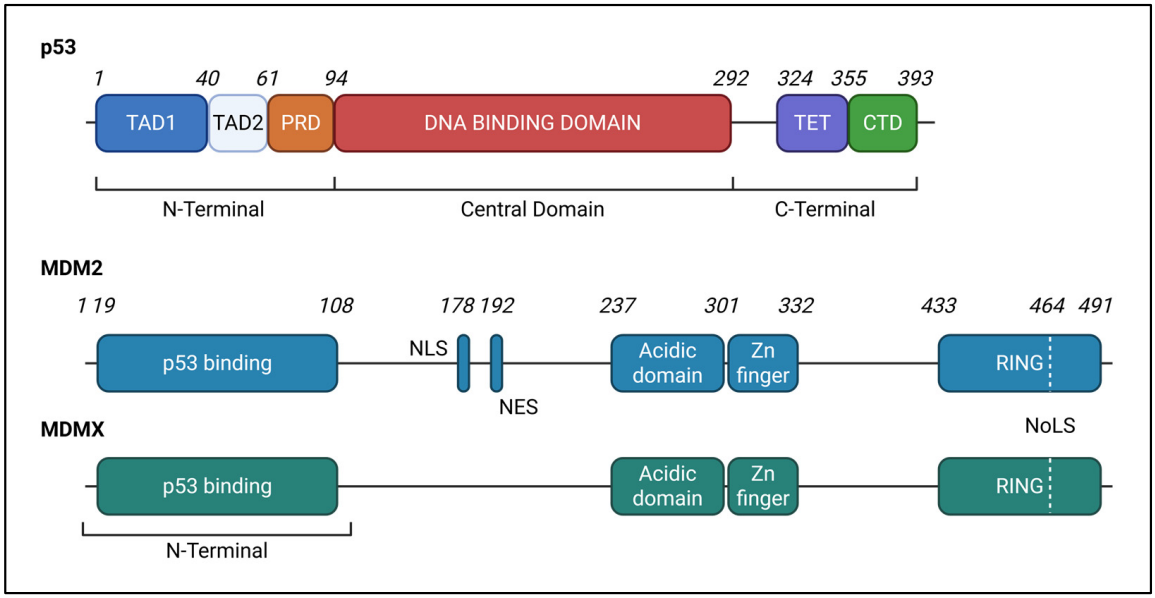

Figure 2. The protein structure of p53 and its regulators Mdm2 and MdmX. The human p53 protein is 393 amino acids in length, consisting of an N-terminal, central domain and C-terminal. The N-terminal, composed of the TAD1 and two domains and a proline-rich domain (PRD), has the main function of interacting with transcription machinery components and transcriptional coactivators, as well as p53 negative regulators. The central domain is required for recognising sequence-specific target DNA, the main physiological function of p53. The C-terminal domain includes a TET domain required for forming p53 tetramers, and the CTD domain that has regulatory functions including DNA binding, cofactor recruitment, cellular localization, and protein stabilization. Mdm2 and MdmX

are the major negative regulators of p53, and are homologues to each other, being 491 amino acids in length. Both proteins consist of an N-terminal for binding to p53 proteins, an acidic domain, a zinc finger domain, and a RING domain. However, MdmX lacks the NLS and NES sites, so cannot be translocated to the nucleus, as well as lacking ubiquitin ligase activity. Abbreviations: CTD, C-terminal regulatory domain; Mdm2, Mouse DoublMinute 2 homolog; MdmX, Mouse Double Minute X homolog; NES, nuclear export signal; NLS, nuclear localisation signal; NoLS, nucleolar localisation signal; PRD, proline-rich domain; TAD, trans-activating domain; TET, tetramerization domain. Figure created with BioRender.com.

Given that p53 is a master regulator of multiple cellular processes, it requires tight regulation of its activities at DNA, RNA, and protein levels to prevent excessive activation of its downstream target genes. To maintain balanced cellular p53 protein levels and preserve normal cell cycle regulation, p53 is tightly modulated by the structural homologues Mdm2 and mouse double minute X (MdmX (also known as Mdm4)), which function either independently or as a heterodimer to negatively regulate p53 transcriptional activity (Figure 1). Notably, Mdm2 itself is a transcriptional target of p53: p53 activation induces transcription of the *MDM2* gene, forming an autoregulatory feedback loop that limits p53 protein levels.

Within the nucleus, Mdm2 binds to p53 through hydrogen-bond interactions to form a complex that prevents p53 from interacting with transcriptional co-activators, thereby repressing gene expression. This interaction also promotes nuclear-to-cytoplasmic export of phosphorylated p53. Once exported, Mdm2 acts as an E3 ubiquitin ligase through its RING domain and zinc finger, targeting p53 for proteasomal degradation and reducing p53 protein levels [37]. Mdm2 and MdmX share several structural motifs required for p53 binding, including an acidic domain, a zinc finger motif and a RING domain. However, MdmX lacks a nuclear localisation signal and does not possess intrinsic E3 ligase activity (Figure 2). As such, MdmX regulates p53 activity primarily through direct binding to p53 or through formation of homo- or heterodimers with Mdm2 [38]. Formation of an Mdm2-MdmX heterodimer through RING-RING interactions results in a more stable complex than with either homodimer alone, thereby enhancing the ubiquitin ligase activity of Mdm2 and further regulating p53 transcriptional activity. Mdm2 is also capable of ubiquitinating itself and MdmX, providing an additional mechanism for fine-tuning regulation of the p53 pathway.

2.1. Dysregulation of the p53 Pathway

Mutations in the *TP53* gene are commonly associated with human cancers [39], and typically encode a full-length but destabilised and functionally inactive protein with reduced affinity for its target genes. Most cancer-associated mutations are missense loss-of-function (LOF) mutations. These mutations occur predominantly within the DBD of *TP53* and result in structural defects that reduce the kinetic and thermodynamic stability of p53, with loss of transcriptional activity [9]. Among these mutations, six hotspot mutations, R175H, G245S, R248Q/W, R249S, R273C/H, and R282W, are particularly notable, and together account for 30% of all missense mutations [40]. These mutations produce proteins that are unable to induce apoptosis and senescence. Consequently, mutant p53 fails to halt the cell cycle or trigger cell death, resulting in uncontrolled malignant cell proliferation and often promoting a more aggressive tumour phenotype associated with a pro-tumorigenic immune microenvironment.

In addition to loss of tumour-suppressive activity, *TP53* mutations can also confer oncogenic gain-of-function (GOF) properties. In this context, mutant p53 proteins can interact with and modulate transcriptional activities normally associated with wild-type p53 signalling, thereby driving tumorigenesis and therapeutic resistance. GOF mutant p53 proteins can bind with sequence-specific p53 response elements within target genes,

leading to either activation or repression of genes involved in the control of proliferation, apoptosis and malignancy, thereby conferring a selective advantage to tumour cells. Beyond transcriptional regulation in the nucleus, mutant p53 proteins can also interact with intracellular proteins involved in key oncogenic pathways that support proliferation, invasion and metastasis of malignant cells.

2.2. Overexpression of p53 Regulators

In addition to loss of p53 activity through oncogenic mutations, overexpression or amplification of Mdm2 has been observed in numerous malignancies including lung, breast, liver, esophagogastric and colorectal cancers [41]. Such mutations often correlate with a more aggressive phenotype and poorer patient survival. Overexpression of Mdm2 contributes to cancer drug resistance with tyrosine kinase inhibitors and immunotherapies [42–46]. Patients with tumours exhibiting Mdm2 overexpression are more likely to develop resistance and hyper progressive disease (HPD) following treatment with immune checkpoint inhibitors (ICIs) such as anti-programmed cell death protein 1 (PD-1) and anti-programmed cell death ligand 1 (PD-L1) [47]. HPD represents a distinct clinical response to immunotherapy in which tumour growth is accelerated following treatment. This phenomenon has been reported to affect approximately 15% of patients with solid tumours [48,49].

3. The p53 Pathway in Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is an aggressive form of liver cancer that accounts for 90% of all primary liver malignancies, resulting in over 800,000 deaths annually [50]. The development of HCC is significantly increased in the presence of cirrhosis, which represents an advanced fibrotic state of the liver arising from a chronic liver disease. Although viral hepatitis remains the leading global cause of liver disease, excessive alcohol consumption, type II diabetes, obesity and metabolic syndrome collectively represent major causes of chronic liver disease and HCC in Europe and the United States.

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously termed non-alcoholic fatty liver disease (NAFLD), accounts for up to 35% of HCC cases worldwide and is associated with hepatic lipotoxocity, insulin resistance, chronic inflammation and certain genetic polymorphisms [51]. MASLD encompasses a spectrum of liver disorders characterised by hepatic fat accumulation, ranging from relatively benign hepatic steatosis to the more aggressive inflammatory condition metabolic dysfunction-associated steatohepatitis (MASH) [52]. MASH-related HCC currently accounts for 20% of HCC cases and is forecasted to increase dramatically, with a predicted rise of 137% in the United States by 2030 [53,54]. Given its distinct molecular and immune characteristics, this is likely to significantly influence future therapeutic strategies.

3.1. p53 in the Development of HCC

The role of p53 within the liver is extensive. It contributes to maintaining genomic integrity during liver regeneration, regulating oxidative stress and lipid metabolism, and controlling hepatocyte proliferation, senescence and apoptosis, thereby providing protection against liver pathologies [55–57].

Hepatitis B virus (HBV) remains, globally, the major aetiological cause of HCC and its regulatory protein HBx functions as a viral oncogene [58]. HBx can directly bind to Mdm2, block its ubiquitination, and thereby increase expression and nuclear import of p53 (Figure 3). One consequence of this interaction is transcriptional activation of the MDM2/CXCL12//CXCR4/β-Catenin pathway, which promotes stem-like properties of

cancer-stem-like cells [59]. Additionally, HBx can bind directly to p53 to promote its translocation to the cytoplasm to disrupt DDR mechanisms and promote HCC development [58].

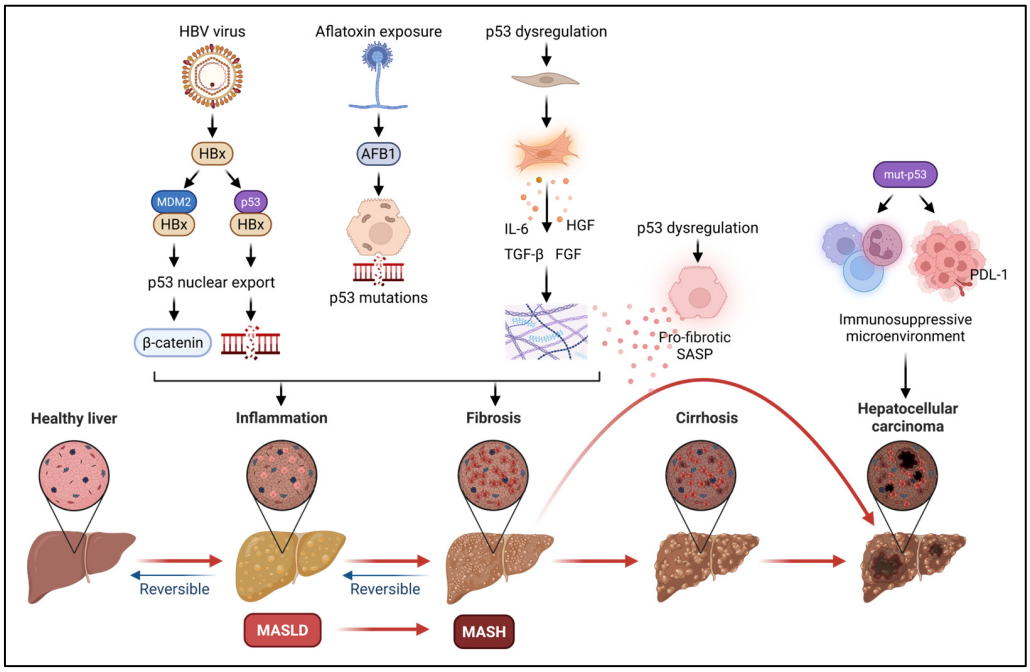

Figure 3. Schematic of the roles of p53 in the development of HCC. p53 plays a role in creating an inflammatory and fibrotic liver microenvironment that promotes HCC development. The oncogene HBx, in patients with HBV, can bind to both Mdm2 and p53. The former binding promotes p53 nuclear export and activation of the β-catenin pathway to promote cancer stemness. HBx binding to p53 disrupts the DDR and DNA mutations. Aflatoxin exposure (AFB1) also promotes HCC development in a p53-manner, whereby hepatocytes metabolize AFB1, resulting in T53 mutations. Fibrosis underlies many HCC cases and is increased when p53 activity is dysregulated, promoting myofibroblast activation and disruption of liver tissue architecture. Dysregulation of p53 activity also promotes a pro-fibrotic and pro-tumorigenic SASP from hepatocytes. In the HCC tumour microenvironment, mutant p53 or dysregulation of p53 activity promotes the influx of immunosuppressive immune cells into tumour sites, as well as the upregulation of PD-L1. Abbreviations: AFB1, aflatoxin B1; FGF, fibroblast growth factor; HGH, hepatocyte growth factor; HBV, hepatitis B virus; HBx, hepatitis B protein; IL-6; interleukin 6; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; PD-L1, programmed cell death ligand 1; SASP; senescence-associated secretory phenotype; TGF-β, transforming growth factor-beta. Figure created with BioRender.com.

Another major risk factor for HCC is exposure to aflatoxin B1 (AFB1), a mycotoxin produced by *Aspergillus flavus* and *Aspergillus parasiticus*, commonly found in contaminated grains and nuts. Around 5–28% of HCC cases worldwide are related to AFB1 exposure [60]. In hepatocytes, AFB1 is metabolized by cytochrome P-450 enzymes into an epoxy-aflatoxin intermediate that binds with DNA to induce oncogenic mutations. A characteristic mutation associated with AFB1 exposure is a G-to-T transversion at codon 249 of *TP53*, resulting in the substitution of arginine for serine (R249S) in the p53 protein [61] (Figure 3). This missense mutation occurs in approximately 10% of HCC cases [62], and is associated with upregulation of stem cell-like genes such as *NANOG*, *OPOU5F1*, *SOX2*, and *c-MYC*. Patients harbouring this mutation often exhibit more aggressive tumour phenotypes and poorer clinical outcomes [63]. For some individuals, HBV infection and AFB1 exposure act synergistically to accelerate HCC development. This combination of exposures can create a highly proinflammatory hepatic environment in which mutated hepatocytes evade cell death [64], increasing the risk of HCC development up to 30-fold [65].

Advanced fibrosis, which underlies over 80% of HCC cases [66], can be promoted when p53 activity is lost or dysregulated. Hepatic p53 has been shown to interact with fibrogenic signalling pathways such as TGF-β to influence the initial progression of fibrosis [67] (Figure 3). The p53 pathway also stimulates the transdifferentiation of hepatic stellate cells (HSCs) into activated myofibroblasts, which represent the major cell type responsible for excessive deposition of fibrotic extracellular matrix (ECM) [68,69]. This accumulation of ECM proteins, such as collagen type I and III and fibronectin, alongside the matrix regulating MMPs and TIMP-1, leads to profound disruption of liver tissue architecture and alterations in the composition and quantity of the hepatic ECM. These changes ultimately contribute to progressive scar-tissue formation.

Fibrotic/cirrhotic tissue can establish tissue microenvironments in which there is an increased risk of genomic instability that may promote oncogenic processes. The fibrotic liver represents a highly inflamed microenvironment characterised by elevated production of ROS from resident liver cells including activated stellate cells, hepatocytes and Kupffer cells. This oxidative stress can induce DNA damage and promote cancer-associated mutations [70,71]. Another contribution to the inflammatory and fibrotic liver microenvironment is the release of pro-inflammatory cytokines such as TGF-β, IL-6 and TNF-α from HSCs, Kupffer and immune cells. These cytokines reinforce chronic inflammation, fibrotic stress, and oxidative stress [70,72]. Furthermore, fibrotic and cirrhotic environments are highly proliferative, with rapid hepatocyte death and regeneration, creating substantial replicative stress. This increases the likelihood of replication errors, chromosomal instability and clonal expansion of premalignant cells [73,74].

Under normal physiological conditions, liver injury promotes activation of HSCs into a senescent phenotype, resulting in the release of a SASP-like secretome with fibrotic properties. However, when p53 activity is impaired, for example during HBV infection, HSCs can enter a dysfunctional state of senescence characterised by an exaggerated pro-tumorigenic and pro-fibrotic SASP that evades immune surveillance and promotes a pro-tumorigenic cirrhotic microenvironment [75,76] (Figure 3).

3.2. Mutated p53 in HCC

TP53 mutations occur in approximately 25–30% of HCC tumours [77]. The presence of mutant p53 in HCC is frequently associated with an altered immune microenvironment characterised by increased numbers of immunosuppressive cell populations and elevated expression of immune checkpoint molecules [78]. *TP53* mutations may also serve as prognostic markers, as they are associated with poor responses to ICIs and increased risk of tumour recurrence [79,80].

As discussed above, the major *TP53* hotspot mutations observed in HCC include R175H, G245S, R248Q/W, R249S, R273C/H, and R282W. These mutations represent either DNA contact or structural mutations, which produce varying degrees of genomic instability and contribute to HCC pathogenesis. DNA contact mutations impair p53-DNA binding without disrupting the overall protein structure. Mutations such as R248Q/W and R273H fall into this category, and represent relatively rare hotspot mutations in HCC [62]. Consequently, investigations examining the genotype–phenotypes of these mutations remains limited. However, in other cancer types, R248Q/W and R273H mutations are commonly associated with invasive phenotypes characterised by enhanced migration, invasion and epithelial–mesenchymal transition (EMT) pathways [81–83]. Other common hotspot mutations in HCC are structural mutations such as R175H, G245S, and R249S, which result in misfolded GOF p53 proteins that promote tumour drug-resistance, inflammation, angiogenesis, and metabolic reprogramming [34,84].

In addition to *TP53* mutations, overexpression of the p53 regulators Mdm2 and MdmX has also been observed in HCC, and is associated with persistent suppression of p53 activity. This dysregulation contributes to both tumorigenesis and resistance to therapy [10,85,86]. Consequently, the p53/Mdm2 axis in HCC represents a promising therapeutic target in HCC.

4. p53 and Its Role in the HCC Tumour Microenvironment

The TME is a complex multicellular ecosystem composed of tumour cells, infiltrating immune cells, stromal cells, and the tumour-associated ECM. These components interact through networks of chemokines, cytokines, growth factors and inflammatory mediators, to shape the immune and metabolic landscape of the tumour, which has potential to evolve immune-suppressive niches that enable immune evasion. Across many malignancies, the TME is heavily infiltrated by pro-tumour immune cells, such as macrophages and regulatory T cells (Tregs) and, in addition, stromal cells known as cancer-associated fibroblasts (CAFs). These cells secrete inflammatory mediators that remodel the immune landscape and facilitate tumour immune evasion. Emerging evidence suggest that *TP53* mutations and dysregulation of downstream signalling pathways contribute to inflammation, tumorigenesis and immune evasion in a variety of cancers, such as those arising in the inflamed liver, colon and pancreas [87,88]. These findings suggest that *TP53* mutations may contribute to immune editing of the TME, favouring expansion of tumour cell clones capable of evading immune surveillance.

Beyond its classical roles, p53 also exerts effects on cellular metabolism, which may have important implications for TME evolution. In hepatocytes, p53 regulates multiple metabolic pathways, including glycolysis, oxidative phosphorylation, fatty acid oxidation and antioxidant responses [89]. Loss of p53 function can therefore promote metabolic reprogramming that favours tumour growth, including increased glycolysis and lipid synthesis. In the context of HCC, these alterations may further shape the TME by influencing immune cell recruitment, cytokine production and nutrient competition, within the tumour niche. As a result, dysregulation of p53-dependent metabolic pathways may contribute not only to hepatocyte transformation, but also to development of an immunosuppressive microenvironment that supports tumour progression.

4.1. Inflammation

Chronic inflammation is a hallmark of cancer and serves as a major driver of tumorigenesis by creating microenvironments that promote malignant transformation. This is particularly relevant in HCC, where chronic inflammation resulting from viral infection, alcohol toxicity and metabolic dysregulation lead to sustained production of ROS, reactive nitrogen species (RNS), and pro-inflammatory mediators. These factors damage DNA, disrupt DNA repair mechanisms and increase genetic instability, thereby promoting cancer development [90]. A key inflammatory pathway activated in HCC is the IL-6/Signal transducer and activator of transcription 3 (STAT3) axis. In this pathway, secretion of IL-6 activates STAT3, which in turn regulates inflammatory responses in immune cells, as well as tumour cells, where it promotes proliferation, invasion and metastasis [91]. Previous studies demonstrated that wild-type p53 functions in regulating the IL-6/STAT3 axis to promote cell cycle arrest and apoptosis. Loss of wild-type p53 or the presence of LOF mutant p53 results in STAT3 dysregulation and hyperactivation of STAT3 signalling. This process facilitates ECM degradation, angiogenesis, and tumour infiltration by pro-tumour immune cells such as M2 macrophages and Tregs [92,93]. Conversely, in cancers where IL-6/STAT3 signalling is constitutively activated, phosphorylated STAT3 can negatively reg-

ulate wild-type p53 by binding to *TP53* promoter to repress transcription of pro-apoptotic genes, thereby promoting survival of malignant cells [94,95].

The role of Nuclear Factor kappa-B (NF-κB) signalling in liver inflammation, fibrosis and cancer has been extensively documented [96,97]. NF-κB signalling is robustly activated in the context of chronic liver injury, and stimulates the establishment of proinflammatory microenvironments that contribute to genetic instability by inhibiting programmed cell death. NF-κB and p53 frequently operate in an antagonistic regulatory relationship. Elevated NF-κB signalling suppresses p53 transcriptional activity through upregulation of Mdm2, whereas activation of p53 can suppress NF-κB signalling [96]. When p53 is mutated or its activity is suppressed, NF-κB signalling becomes hyperactive, resulting in chronic inflammation driven by soluble factors such as IL-1β, IL-6 and TNF. These factors contribute to hepatocyte injury, regenerative proliferation, and fibrogenic activation of stellate cells [98].

4.2. Role of Senescence and the SASP

Cellular senescence is an important biological process in the progression of chronic liver disease to HCC. Under conditions of persistent inflammation, such as that observed in chronic liver disease, senescence can be induced in hepatocytes and other liver cell types. Triggers for senescence include oxidative stress, oncogene activation, and cellular damage resulting from radiation or chemotherapy. These stress signals activate the DDR, leading to activation of p53 and its downstream targets p21 and Rb, leading to cell cycle arrest. Senescence represents a biological paradox in the liver. It initially acts as a tumour-suppressive barrier, preventing proliferation of damaged hepatocytes and promoting immune clearance. However, persistent senescence and accumulation of senescent cells during chronic liver disease can instead create a pro-tumorigenic microenvironment. In the early stages of liver disease, the hepatocellular SASP can promote tissue repair. For example, secretion of CCL2 stimulates monocyte recruitment, while TGF-β promotes fibrogenesis. Senescence also acts as an anti-tumoral mechanism by halting proliferation of transformed hepatocytes and recruiting immune cells, including T cells, macrophages and natural killer (NK) cells. This immune response eliminates damaged senescent cells and prevents progression to HCC [99]. The importance of this protective mechanism is highlighted by the observation that mutations in the telomerase (TERT) promoter that enable senescence escape are present in up to 60% of HCC tumours [80].

Numerous studies have demonstrated that restoration of p53 activity can elicit anti-tumour response in liver cancer models through induction of a senescence [100–102]. As an example, Xue et al. found that restoration of p53 activity using RNAi resulted in hepatocellular senescence characterised by decreased proliferation and positive β-galactosidase staining [100]. The induction of senescence triggered an innate immune response involving increased expression of *Csf1*, *Mcp1*, *Cxcl1* and *Il15*, which was associated with increased recruitment of neutrophils, macrophages and NK cells, with promotion of anti-tumour immunity. Similar observations were reported by Iannello et al., who showed that p53 reactivation increased chemokines such as CCL1, CCL4 and CCL5, and was accompanied by recruitment of NK cells to eliminate senescent cells and suppress tumour progression [102].

In the context of chronic liver injury, senescence may also promote HCC tumour development [103]. Persistent DDR activation in hepatocytes and stellate cells can promote chronic SASP production, leading to sustained inflammation and genotoxic stress within the liver. SASP signalling can further induce senescence in neighbouring cells to amplify damage and inflammatory signalling [99]. Senescence may also promote tumour aggressiveness through induction of stem cell-associated gene expression, particularly in patients who have previously received chemotherapy and later develop recurrent disease [104].

Although the relationship between cellular senescence and HCC pathogenesis has been highly explored, the connection between senescence and tumour mutational burden (TMB) is less well understood. Chronic inflammation and ageing-related inflammatory processes ("inflammaging") may contribute to increased mutational burden in liver cells [105,106] which could potentially influence tumour evolution and disease progression.

4.3. T Cells and Immune Checkpoint Expression

T cell-mediated immune responses play a critical role in tumour cell surveillance and elimination. The infiltration of lymphocytes into the TME can be used to classify tumours as "cold" (immune excluded) or "hot" (immune-inflamed), this immune landscape being strongly influenced by p53 mutation status. Recent studies have shown that HCC tumours harbouring *TP53* mutations frequently exhibit immunosuppressive TME characterised by decreased lymphocytic abundance [78,107,108]. Veeraiyan et al. demonstrated that cancer cells carrying *TP53* missense mutations activated STAT3 signalling, promoting recruitment of neutrophils and Tregs into the HCC TME, together with increased expression of inflammatory markers including S100A8, ARG1, CCL17 and CCL22 [108]. Neutrophils can promote HCC progression through multiple mechanisms, including immunosuppression, direct enhancement of tumour cell survival, enhanced invasiveness and metastatic capacity, increased extracellular matrix remodelling, and angiogenesis [109]. One key mechanism by which neutrophils promote immunosuppression is through expressing PD-L1, which inhibits cytotoxic T cell activity. Similar findings were reported by Long et al., who identified differential expression of 37 immune-response related genes in *TP53*-mutant tumours. The TME of these tumours exhibited increased Tregs, non-activated M0 macrophages, and elevated immune checkpoint expression [78]. More recently, decreased $CD4^+$ memory T cell infiltration, together with increased macrophages, Tregs, and $CD8^+$ T cells, was reported in *TP53*-mutant tumours [110]. Collectively, these studies suggest that mutant p53 proteins can contribute to the evolution of an immunosuppressive TME that promotes tumour progression and may also impair immunotherapy.

An important mechanism by which tumours evade immune surveillance is through the PD-1/PD-L1 axis. PD-L1 expressed on tumour cells binds to PD-1 on $CD8^+$ T cells, inhibiting their cytotoxic activity and enabling immune evasion. PD-L1 expression can be regulated at genetic, epigenetic, and transcriptional levels, and may be influenced by p53 signalling. In several tumour models, restoration of wild-type p53 using Mdm2 inhibitors has been reported to increase PD-L1 expression [111–113]. One proposed mechanism involves activation of the interferon-γ/JAK/STAT/IRF1 pathway following secretion of IFN-γ by activated T cells and NK cells [114,115]. Thiem et al. demonstrated that p53 mutations influenced IFN-γ-induced PD-L1 expression in melanoma cells, with p53 knockdown resulting in diminished levels of PD-L1 [116]. Although the relationship between p53 and the IFN-γ/JAK/STAT/IRF1 pathway has not been fully investigated in HCC, activation of this pathway has been reported in HCC cells and correlated with PD-L1 expression [117,118]. Loss of p53 function may also activate the mammalian target of the rapamycin (mTOR) pathway, resulting in enhanced E2F1 transcriptional activation of the PD-L1 gene [119].

4.4. Cancer-Associated Fibroblasts (CAFs)

CAFs are abundant stromal cells within the HCC microenvironment that cross talk with both cancer cells and immune cells to promote tumorigenesis, immunosuppression, and invasion. CAFs secrete multiple mitogenic factors including IL-6, TGF-β, hepatocyte growth factor (HGF) and fibroblast growth factor (FGF), as well as a plethora of cytokines that stimulate EMT and the production of ECM proteins, resulting in a TME with increased

stiffness [120]. The relationship between p53 and CAFs within the HCC TME is poorly understood, but has been explored in other cancers. Using a prostate cancer xenograft model with a *TP53* mutation at N236S, CAF-specific factors such as α-smooth muscle actin (α-SMA), vimentin, and CXCL12 were upregulated. This promoted CAF activation with in vitro experiments demonstrating increased migratory and invasion potential of the p53 mutant tumour cells [121]. *TP53* mutations may therefore promote CAF activation and deposition of collagen and other stromal factors, to promote prostate cancer progression and aggression. In ovarian cancer models, repression of CAF p53 activity stimulated an inflammatory phenotype characterised by elevated levels of IL-1β, IL-6, GRO-α, IL-1α, IL-8, and VEGF in the TME [122]. Knockdown of p53 increased in vivo xenograft ovarian cancer growth, with the inflammatory phenotype being dependent on NF-κB signalling. Hence, both wt and mutant p53 may have consequential effects on fibroblasts in the TME resulting in repression or promotion of tumour progression, and, as such, CAF-expressed p53 in HCC is worthy of future investigation.

4.5. Macrophages

Tumour-associated macrophages (TAMs) are key regulators of tumour progression, contributing to immunosuppression, invasion, metastasis, EMT, cancer stemness, and chronic liver inflammation. Macrophages can adopt either anti-tumour or pro-tumour phenotypes, broadly termed M1 and M2 macrophages, respectively. These populations shape the tumour immune microenvironment through the secretion of cytokines and mediators, including tumour necrosis factor-α (TNF-α), IL-1β and IL-6 (associated with anti-tumour activity), and IL-10, TGF-β, vascular endothelial growth factor (VEGF), and matrix metalloproteinase-9 (MMP9), which promote tumour progression [93–95]. Macrophage polarisation is highly plastic and is regulated by signals derived from the surrounding microenvironment, as well as autocrine signalling pathways.

Evidence suggests that p53 plays an important role in regulating macrophage phenotype. Li et al. demonstrated that activation of p53 through inhibition of Mdm2 suppresses M2 polarisation, as shown by reduced expression of M2-associated genes including *Irf4*, *c-Myc*, *Arg1* and *Retnla*. In contrast, macrophage-specific loss of p53 increased expression of these genes and enhanced M2 macrophage proliferation [96]. p53 signalling may also influence macrophage polarisation indirectly, through effects on stromal cells. In HCC associated with liver fibrosis and cirrhosis, activation of p53 in HSCs induces cellular senescence and the SASP [97]. Cytokines released as part of the SASP, including IL-6 and IFN-γ, appear to skew resident macrophages away from a pro-tumour phenotype, characterised by reduced expression of M2-associated genes and increased M1 markers.

Conversely, loss of p53 in tumour cells can promote macrophage-mediated immunosuppression. Nian et al. demonstrated that *TP53* knockout in liver cancer models induces secretion of IL-34 from cancer stem cells into the tumour microenvironment, suggesting that wild-type p53 normally represses *IL34* transcription [98]. Elevated IL-34 levels correlated with increased macrophage infiltration and enrichment of M2-associated gene signatures, including *Ccl2*, *Il10* and *Arg1*. Furthermore, 293T cells expressing the *TP53* R249S hotspot mutation, commonly associated with aflatoxin B1 exposure, failed to repress *IL34* expression in luciferase reporter assays, indicating that this mutation functions as a loss-of-function variant.

Together, these findings suggest that disruption of p53 signalling promotes an immunosuppressive tumour microenvironment by enhancing IL-34-driven M2 macrophage polarisation and suppressing T cell-mediated immunity. More broadly, these studies highlight the complex and context-dependent roles of both wild-type and mutant p53 in shaping macrophage behaviour within the HCC tumour microenvironment.

5. Therapeutic Targeting of the p53 Pathway

Decades of research demonstrate the pivotal role of the p53 pathway in both cancer progression and senescence. As a result, modulation and activation of p53 represent promising therapeutic strategies. At present, three main therapeutic strategies are under investigation to target both wild-type and mutant forms of p53: (1) blocking the interaction between wild-type p53 and Mdm2, (2) blocking both Mdm2 and MdmX, and (3) strategies designed to overcome or restore the dysfunctional activities of mutant p53 proteins (Figure 4).

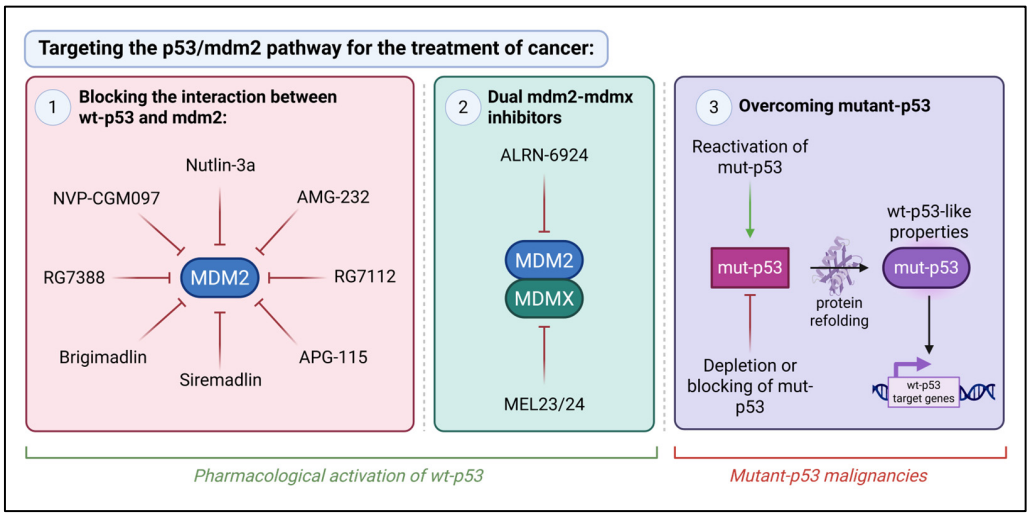

Figure 4. Targeting the p53/mdm2 pathway for the treatment of HCC. The main therapeutic strategies are under investigation for targeting both wt and mutant forms of p53: (1) blocking the interaction between wt p53 and Mdm2, (2) blocking both Mdm2 and MdmX, and (3) strategies that overcome the mutant activities of p53 by refolding the mutated protein to regain wt p53 properties or by blocking the activities of mutant p53. Figure created with BioRender.com.

5.1. Small Molecules Directly Targeting the p53-Mdm2 Interaction

Nutlins:

Some of the first small molecules identified to disrupt the Mdm2-p53 interaction were the nutlins, a group of cis-imidazoline analogues that bind to three key sub-pockets within the hydrophobic cleft of the Mdm2 N-terminus [123,124]. In preclinical models of HCC, nutlins promote tumour cell apoptosis, as demonstrated by increased levels of cleaved caspase-3 and caspase-7 [125,126]. This activity may explain the ability of nutlins to enhance the cytotoxic effects of other anti-cancer drugs such as doxorubicin and cisplatin, particularly in previously drug-resistant cancer cells [127–129]. In HCC and oesophageal cancer models, treatment with nutlin-3, a more potent nutlin, induced upregulation of p53 and activation of the intrinsic apoptotic pathway, as demonstrated by increased of puma and noxa [129,130]. When combined with other cancer therapy agents, nutlin-3 acts synergistically to inhibit tumour growth, enhance anti-cancer efficacy, and potentially reduce treatment-associated toxicity.

Based on the structure framework of the nutlins, second-generation Mdm2 inhibitors such as RG7112 and RG7388 were subsequently designed and clinically evaluated. Several phase I clinical trials have investigated these compounds in both solid and haematological malignancies [131–135], following promising in vitro and in vivo studies demonstrating their ability to activate p53 and induce tumour cell death [136–139]. These inhibitors have also been shown to re-sensitise drug-resistant malignant cells to therapy [140,141].

RG7388, also known as idasanutlin, is a more potent and selective Mdm2 inhibitor, with a superior pharmacokinetic profile compared to RG1772. However, it has not yet been

evaluated in HCC. Studies using in vitro and in vivo liver cholangiocarcinoma models have demonstrated that when combined with a wild-type p53-induced phosphatase 1 (WIP1) inhibitor, RG7388 enhanced p53 activity, leading to significant inhibition of tumour growth [142]. However, like most Mdm2 inhibitors, RG7388 has a toxicity profile involving neutropenia and thrombocytopenia which can cause severe reactions and discontinuation of drug regimens for some patients [143].

APG-115:

Another small-molecule inhibitor that has recently attracted attention is the spiro-oxindole APG-115 (alrizomadlin), which contains an indole ring capable of forming hydrogen bonds with Mdm2 and thereby inhibiting its activity [39]. Recent in vitro and in vivo studies demonstrated that APG-115 inhibits cellular proliferation at nanomolar concentrations, induces cell cycle arrest at the G0/G1 phase, and stimulates apoptosis [111,112,144–147]. When combined with PD-1 blockade, APG-115 was shown to modulate the immune response in both p53 wild-type, mutant, and deficient syngeneic liver tumour models, increasing the infiltration of $CD8^+$ T cells and M1 macrophages into the TME [112]. Combined treatment with APG-115 and anti-PD-1 suppressed M2 macrophages, while increasing $CD25^{high}CD62L^{low}$ T cell populations, representing activated or effector T cells. Additionally, this treatment increased tumour cell expression of PD-L1. APG-115 has also demonstrated promising results in a phase I clinical trial as a monotherapy for patients with either wild-type or mutant p53 solid tumours [145]. Several trials are currently underway to evaluate APG-115 in combination with inhibitors of PD-1, MEK and Bcl-2, and the chemotherapy agent azacitidine [148–154].

AMG-232:

Another class of Mdm2 inhibitors includes the stilbenes, which contain meta-chlorophenyl, para-chlorophenyl, and c-chain isopropyl moieties that interact with Mdm2 and inhibit p53 degradation [37]. AMG-232 is a potent and selective member of this class that has undergone phase I clinical investigation in several malignancies including melanoma, acute myeloid leukaemia, and solid tumours [155–157]. Preclinical studies demonstrated that AMG-232 inhibits cellular proliferation in a p53-dependent manner across both malignant cell lines and patient-derived tumour models. RT-qPCR analysis revealed increased expression of p53 target genes including *p21*, *BAX* and *PUMA*, with treated cells undergoing cell cycle arrest in the G0/G1 phase [158]. Importantly, sensitivity to AMG-232 sensitivity depends on *TP53* mutation status, with p53 mutated cells generally being insensitive even at high drug concentrations.

5.2. Dual Inhibitors of p53 Regulators

Recent research has shifted towards next-generation p53-targeted therapeutics capable of disrupting both Mdm2 and MdmX and thereby enhancing the anti-tumour transcriptional activity of p53. The dual Mdm2/MdmX antagonist ALRN-6924 (Sulanemadlin) is a stapled α-helical peptide, originally discovered in 1988 [159]. This molecule can penetrate cells and bind with high affinity to both Mdm2 and MdmX by mimicking the N-terminal α-helical of p53 [160]. ALRN-6924 has demonstrated strong in vitro and in vivo activity across multiple malignancies, effectively blocking the Mdm2/MdmX-p53 interaction, restoring p53-dependent tumour suppressor activity, and inducing cancer-cell cycle arrest and apoptosis [161,162]. Similar to other Mdm2 inhibitors, ALRN-6924 may also be used in combination with other anti-cancer drugs to enhance tumour cell killing, and may offer advantages compared with inhibitors targeting Mdm2 alone [160,163]. However, its efficacy and clinical relevance have yet to be evaluated in the context of HCC.

5.3. Targeting Mutant p53

Because more than 50% of cancers harbour *TP53* mutations, the development of compounds capable of targeting mutant p53 proteins represents an important area of drug discovery. Strategies aimed at restoring wild-type p53 activity in mutant p53 proteins fall into three categories: (1) stabilisation of wild-type protein conformation by preventing mutant p53 aggregation, (2) refolding mutant p53 to restore wild-type target gene transcription, and (3) exploiting synthetic lethality associated with mutant p53.

One of the earliest compounds identified to restore wild-type function in mutant p53 proteins is CP-31398, a styrylquinazoline compound that activates the p53 pathway and induces tumour cell death both in vitro and in vivo, as demonstrated by increased p53, p21, and cleaved caspase-3 [164,165]. Despite promising early findings, CP-31398 was shown to have off-target effects, suggesting it may target other cellular proteins independent of p53 signalling [166,167]. Consequently, CP-31398 has not progressed to clinical evaluation.

Another compound targeting mutant p53 is the alkylating agent PRIMA-1, which acts as a Michael acceptor and covalently binds cysteine residues within the p53 core domain, inducing confirmational changes of the protein [168,169]. Binding of PRIMA-1 to Cys124 and Cys277 promotes refolding of mutant p53 into a conformation more closely resembling the wild-type protein, thereby restoring wild-type transcriptional activity and inducing cell cycle arrest and apoptosis in HCC tumour cells [170,171]. However, PRIMA-1 and its derivative APR-246, are not entirely specific for mutant p53, and can form covalent adducts with cysteine residues in other proteins including thioredoxin reductase and glutathione, which are abundant in liver tissue [172,173]. Therefore, the observed anti-cancer effects of these compounds may also occur in tumours lacking mutant p53, highlighting their broader therapeutic potential, independent of p53 mutational status.

5.4. Combined Treatment with Immunotherapies

The development of immunotherapy has transformed cancer treatment by enabling therapeutic activation of the host immune system to eliminate malignant cells. ICIs, including antibodies targeting the PD-1/PD-L1 axis and cytotoxic T-lymphocyte associated protein 4 (CTLA-4), enhance and sustain T cell-mediated anti-tumour immunity and have demonstrated efficacy in HCC. However, response rates to ICI monotherapy are modest, with fewer than 20% of patients achieving durable responses, and, unfortunately, a subset developing HPD. This limited efficacy reflects considerable heterogeneity in the immune landscape of the HCC TME. Tumours arising within the same disease context can exhibit profoundly different immune constituents, which leads to substantial variation in the immune therapeutic response.

Mechanisms contributing to ICI resistance include inadequate infiltration of lymphocytes and other effector cells, impaired drug delivery arising from a disordered tumour vasculature, tumour ECM-mediated exclusion of immune cells, high numbers of immunosuppressive cells, and the emergence of adaptive drug-resistance mechanisms within tumour cells [174]. The composition of the tumour immune microenvironment is a major determinant of ICI responsiveness. Tumours characterised by strong PD-L1 expression, elevated numbers of tumour-infiltrating lymphocytes, and a high IFN-γ gene signature are generally associated with more favourable prognostic outcomes. In contrast, enrichment of the TME with immunosuppressive Tregs and myeloid-derived suppressor cells (MDSCs), as well as soluble cytokines such as IL-6 which promote tumorigenesis and inhibit apoptosis, are associated with poor clinical outcomes following checkpoint blockade [175].

Emerging evidence suggests that *TP53* mutational status may influence the immune phenotype of HCC tumours and their response to immunotherapy. *TP53* mutant HCC tumours frequently exhibit increased expression of PD-1 or PD-L1 [78,119], indi-

cating these tumours may be particularly sensitive for immunotherapy. In support, in lung adenocarcinoma, *TP53* mutations correlate with increased immune checkpoint expression and good strong clinical benefits after treatment with anti-PD-1 [176,177]. However, the impact of *TP53* mutational status on ICI therapy in HCC remains poorly defined. Future studies should therefore evaluate how different classes of *TP53* mutations, including GOF and LOF, influence the expression of immune checkpoints and responses to immunotherapy.

5.5. Therapeutic Challenges and Future Directions

Despite considerable interest in therapeutic targeting of the Mdm2-p53 axis, clinical development of Mdm2 inhibitors has faced significant challenges. A substantial proportion of clinical trials evaluating Mdm2 inhibitors as monotherapies or in combination regimens failed to progress beyond early-phase development. More than 60% of recent clinical trials investigating compounds such as siremadlin, idasanutlin and sulanemadlin were discontinued, mostly due to funding constraints. Furthermore, approximately 20% of trials were terminated due to inadequate response rates or poor safety profiles including severe adverse events such as grade 4 neutropenia and alopecia (Table 1). As seen in a variety of clinical trials, direct Mdm2 inhibition can result in significant adverse events including cytopenia, gastrointestinal toxicities and metabolic disturbances. These toxicities may be exacerbated when combined with immunotherapy regimes. Navigating the toxicity of Mdm2 inhibitors in HCC therefore presents challenges, as p53 is expressed in both malignant and non-malignant hepatocytes and other resident liver cells. Consequently, systemic activation of p53 through therapeutic targeting of Mdm2 may produce significant on-target toxicities in healthy liver tissue.

Table 1. Previous and current clinical trials investigating monotherapy or combination therapy of Mdm2/MdmX inhibitors to treat various malignancies. Abbreviations: PPI; AML, acute myeloid leukaemia; CML, chronic myeloid leukaemia; DLBCL, diffuse large B-cell lymphoma; ORPBC, oestrogen receptor-positive breast cancer; MDS, myelodysplastic syndrome; N/A, non-applicable; NHL, non-Hodgkin's lymphoma; TNBC, triple-negative breast cancer; NSCLC, non-small-cell lung cancer; SCLC; small-cell lung cancer.

Compound	Chemical Class	Drug Class	Phase	Malignancies	NCT ID	Status
Nutlins	Cis-imidazoline	Small molecule	Preclinical only	N/A	N/A	N/A
RG7112 (RO5045337)	Cis-imidazoline	Small molecule	Phase I	Leukaemia	NCT01677780	Completed
			Phase I	Solid tumours	NCT01164033	Completed
			Phase I	Solid tumours	NCT00559533	Completed
			Phase I	Liposarcomas	NCT01143740	Completed
			Phase I	Hematologic Neoplasms	NCT00623870	Completed
Idasanutlin (RG7388)	Cis-imidazoline	Small molecule	Phase I	Solid tumours	NCT02828930	Completed
			Phase I–II	Myeloma	NCT02633059	Completed
			Phase III	AML	NCT02545283	Terminated
			Phase I–II	DLBCL	NCT03135262	Terminated
			Phase I–II	ORPBC	NCT03566485	Terminated
			Phase I–II	Acute leukaemia or solid tumours	NCT04029688	Terminated
			Phase I	Rhabdoid tumours	NCT05952687	Withdrawn
			Phase I	AML	NCT03850535	Terminated
			Phase I–II	Solid tumours	NCT03362723	Completed
			Phase I	AML	NCT02670044	Completed
			Phase I	NHL	NCT02624986	Terminated

Table 1. *Cont.*

Compound	Chemical Class	Drug Class	Phase	Malignancies	NCT ID	Status
Siremadlin (HDM201)	Imidazolopyrrolidinone	Small molecule	Phase I	Solid and haematological tumours	NCT02143635	Completed
			Phase I–II	AML	NCT05447663	Terminated
			Phase I–II	Soft-tissue sarcoma	NCT05180695	Active, not recruiting
			Phase I	AML	NCT05155709	Terminated
			Phase I	AML	NCT04496999	Terminated
			Phase I	AML or MDS	NCT03940352	Terminated
			Phase I–II	AML	NCT03760445	Withdrawn
			Phase I	Colorectal cancer	NCT03714958	Completed
			Phase I	Liposarcoma	NCT02343172	Completed
Alrizomadlin (APG-115)	Spirooxindole	Small molecule	Phase I–II	Neurofibromatosis	NCT06735820	Active, not recruiting
			Phase I	Neuroblastoma or solid tumours	NCT05701306	Active, recruiting
			Phase I–II	Solid tumours	NCT04785196	Active, recruiting
			Phase II	Leukaemia or NHL	NCT04496349	Active, recruiting
			Phase I–II	AML, MDS or Leukaemia	NCT04358393	Unknown
			Phase I	AML or MDS	NCT04275518	Active, recruiting
			Phase I–II	Salivary gland cancer	NCT03781986	Active, not recruiting
			Phase I–II	Solid tumours or melanoma	NCT03611868	Active, not recruiting
			Phase I	Solid tumours or lymphomas	NCT02935907	Completed
Brigimadlin (BI-907828)	Spirooxindole	Synthetic organic	Phase I	Solid tumours	NCT03449381	Completed
			Phase II	Solid tumours	NCT06619509	Active, not recruiting
			Phase III	Soft-tissue sarcoma	NCT06370871	Withdrawn
			Phase II	Soft-tissue sarcoma, NSCLC, TNBC, colorectal and biliary-tract cancer	NCT06084689	Withdrawn
			Phase III	Liposarcoma	NCT06058793	Completed
			Phase I	Solid tumours	NCT05613036	Completed
			Phase II	Solid tumours	NCT05512377	Completed
			Phase I	Glioblastoma	NCT05376800	Completed
			Phase I	Solid tumours	NCT05372367	Completed
			Phase II–III	Liposarcoma	NCT05218499	Completed
			Phase I	Solid tumours	NCT03964233	Completed
			Phase I	Solid tumours	NCT03449381	Completed
Navtemadlin (AMG-232)	Piperidinone	Synthetic organic	Phase I	Solid tumours or multiple myeloma	NCT01723020	Completed
			Phase I	AML	NCT02016729	Completed
			Phase I	AML	NCT03041688	Active, not recruiting
			Phase I	Brain cancer	NCT03107780	Terminated
			Phase I	Soft-tissue sarcoma	NCT03217266	Completed
			Phase I	AML	NCT04190550	Active, not recruiting
			Phase I–II	CML	NCT04835584	Recruiting
			Phase II–III	Endometrial cancer	NCT05797831	Recruiting
			Phase III	Myelofibrosis	NCT06479135	Recruiting
			Phase I	Multiple myeloma	NCT03031730	Terminated
			Phase I	Melanoma	NCT02110355	Completed
SAR405838 (MI-77301)	Spirooxindole	Small molecule	Phase I	Advanced cancer	NCT01636479	Completed
			Phase I	Solid tumours	NCT01985191	Completed
RITA	Thiophene-furan-thiophene	Small molecule	N/A	N/A	N/A	N/A

Table 1. *Cont.*

Compound	Chemical Class	Drug Class	Phase	Malignancies	NCT ID	Status
PRIMA-1 (APR-246)	Quinuclidinone	Small molecule	Phase I–II	Myeloid tumours	NCT03072043	Completed
			Phase II	AML	NCT03931291	Completed
			Phase III	MDS	NCT03745716	Completed
			Phase I	Myeloid malignancies	NCT04214860	Completed
			Phase I–II	Solid tumours	NCT04383938	Completed
			Phase I	Hematologic or prostate cancer	NCT00900614	Completed
			Phase II	Lymphoma	NCT04990778	Withdrawn
			Phase I–II	NHL or leukaemia	NCT04419389	Terminated
			Phase I–II	MDS or leukaemia	NCT03588078	Unknown
			Phase I–II	Melanoma	NCT03391050	Terminated
			Phase II	Ovarian cancer	NCT03268382	Completed
			Phase I–II	Oesophageal cancer	NCT02999893	Terminated
			Phase I–II	Ovarian cancer	NCT02098343	Completed
MEL23 and MEL24	Alpha-aminobutyric acid	Organic compound	N/A	N/A	N/A	N/A
Milademetan (RAIN-32)	PPI inhibitor	Synthetic organic	Phase I	Solid tumours or lymphomas	NCT01877382	Completed
			Phase I	AML	NCT02319369	Terminated
			Phase I–II	AML	NCT03634228	Terminated
			Phase III	Liposarcoma	NCT04979442	Terminated
			Phase I–II	Solid tumours	NCT06090318	Withdrawn
			Phase II	Solid tumours	NCT05012397	Terminated
NVP-CGM097	Dihydroisoquinolinolinone	Small molecule	Phase I	Solid tumours	NCT01760525	Completed
Sulanemadlin (ALRN-6924)	Stapled α-helical peptide	Peptide inhibitor	Phase I	Paediatric cancer	NCT03654716	Completed
			Phase I	Breast cancer	NCT05622058	Terminated
			Phase I	NSCLC or SCLC	NCT04022876	Terminated
			Phase I	Solid tumours	NCT03725436	Completed
			Phase I	AML or MDS	NCT02909972	Completed
			Phase I–II	Solid tumours or lymphomas	NCT02264613	Completed

A further limitation is that most of the currently available Mdm2 inhibitors require the presence of wild-type p53 for their therapeutic activities. However, approximately 25–30% of HCC tumours harbour *TP53* mutations [77], thus restricting the proportion of patients likely to benefit. Moreover, the functional heterogeneity of *TP53* mutations adds a further layer of complexity, as distinct mutant p53 proteins exert divergent effects on tumour biology and immune function in the TME. Clinical management of HCC is further complicated by the varying levels of hepatic impairment arising from the extent of background liver disease. Cirrhosis alters hepatic architecture and vasculature, generating structural and fibrotic barriers that can impair drug delivery and metabolism and cause increased risk of hepatotoxicity. Additionally, the abnormal and chaotic vasculature of the HCC liver [178], together with its dense fibrotic stroma, can limit drug penetration, promote hypoxia, and contribute to treatment resistance. Taken together, these challenges highlight the need for improved therapeutic strategies that account for the complex interplay between *TP53* status, tumour immune heterogeneity, and the unique pathophysiological context of the cirrhotic liver.

A major challenge in the development of targeted cancer therapies is the emergence of acquired resistance to therapeutic inhibitors, even in patients who initially demonstrate promising responses. In many cases, resistance develops within months, due to the acquisition of mutations in drug-targeted proteins. For example, several studies have shown that prolonged exposure to Mdm2 inhibitors can promote the emergence of p53 mutants, resulting not only in resistance to primary therapy, but also in cross-resistance to other treatment modalities, including chemotherapy [179–182]. One proposed mechanism underlying this phenomenon involves compensatory regulatory

pathways, whereby other p53 regulators function to resist the induction of p53 pro-apoptotic effects induced by Mdm2 inhibitors [182]. Other studies have shown that, along with acquired *TP53* mutations, Mdm2 inhibitor-induced resistance is linked to activation of pro-survival pathways including ERK1/2 and NF-κB [183], as well as upregulation of genes involved in EMT, angiogenesis, and inflammation [184]. Considering this phenomenon, the future targeting of the Mdm2-p53 axis in HCC is likely to rely on rational combinatorial strategies. Mdm2 inhibitors might be combined with chemotherapy agents or ICI, potentially in a sequenced manner, to reduce toxicities and development of *TP53* mutations, while maximising therapeutic benefit. Such strategies may achieve reprogramming of the TME to enhance anti-tumour immune responses.

The mutational status of *TP53* may serve as an important precision medicine tool in guiding therapeutic decision making. As most Mdm2 inhibitors require the presence of wild-type p53 for their activity, relative abundance of wild-type versus mutant p53 is likely to strongly influence therapeutic responses, and ultimately determine the clinical efficacy of p53-targeted therapies. Future therapeutic strategies will therefore require careful patient stratification based on *TP53* status, tumour immune composition, and underlying liver disease, to maximise the clinical benefit of p53-targeted therapies in HCC. Figure 5 summarises the key therapeutic challenges associated with translating drugs targeting the Mdm2–p53 pathway into clinical treatments for patients with HCC.

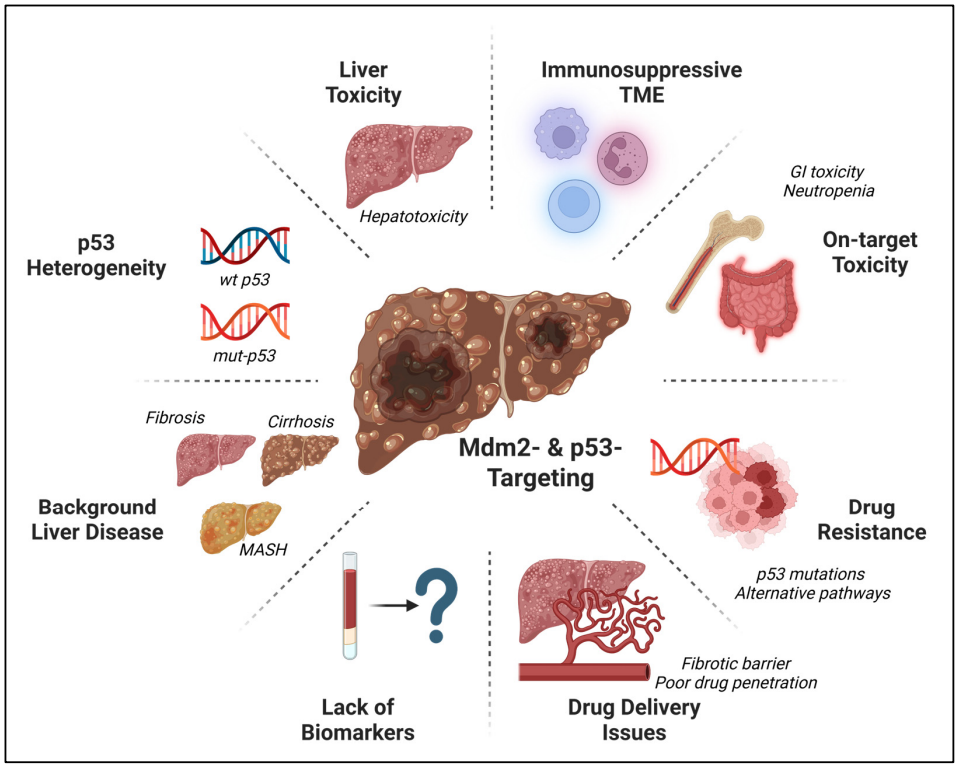

Figure 5. Schematic diagram showcasing the challenges of targeting the p53/mdm2 pathway for HCC patients. The varying p53 heterogeneity is a major problem for Mdm2 inhibitors, as they target wild-type p53, so patients with *TP53* mutations may not respond. Patient underlying background liver diseases, such as fibrosis and cirrhosis, create an unfavourable liver environment that limits drug penetration and increases lipotoxicity. Clinical trials have shown that mdm2 inhibitors can lead to on-target toxicity in healthy cells, with p53 causing gastrointestinal toxicity and neutropenia. Another main challenge for mdm2 inhibitors and p53-targeting drugs is the development of resistance, either through p53 mutations or alternative pathways. Abbreviations: GI, gastrointestinal; MASH, metabolic dysfunction-associated steatohepatitis; Mdm2, mouse double minute 2 homolog. Figure created with BioRender.com.

6. Conclusions

Given the high frequency of *TP53* mutations across many malignancies, it is unsurprising that targeting of the p53/Mdm2 axis has been extensively researched over the past two decades. Both in vitro and in vivo preclinical studies have demonstrated the promising efficacy of Mdm2 inhibitors across multiple cancer types, including HCC, where at least twelve Mdm2 inhibitor compounds have entered clinical trials. The central therapeutic rationale for these approaches is the restoration of p53 activity to induce malignant cell apoptosis and senescence. Beyond these classical tumour-suppressor functions, emerging studies suggest that p53 activation can reshape the HCC TME into a more immunogenic state, promoting the recruitment of immune cells into tumours and enhancing anti-tumour responses. Future therapeutic strategies targeting p53 in HCC patients will likely depend heavily on stratification based on *TP53* mutational status. Tumours harbouring mutant forms of p53 frequently display more aggressive behaviour and resistance to conventional therapies. For these patients, therapeutic approaches capable of restoring wild-type p53 conformation and activity may represent promising strategies. In parallel, combination therapies, for example, pairing Mdm2 inhibitors with immune checkpoint blockade agents to boost cytotoxicity or Bcl-2 family inhibitors to promote more effective tumour cell apoptosis, may play a role in improving efficacy. However, a significant hurdle currently seen in clinical trials is the occurrence of haematological toxicities, particularly neutropenia and thrombocytopenia, but also effects on healthy liver cells expressing wild-type p53. Addressing these toxicities will be critical for development of next-generation Mdm2 inhibitors. One potential strategy to overcome these limitations may involve the design of dual Mdm2/MdmX inhibitors. Another promising approach involves therapeutic sequencing, whereby transient Mdm2 inhibition is used to remodel the tumour immune microenvironment prior to the administration of immune checkpoint inhibitors. Such strategies may convert immunologically 'cold' tumours into more immunotherapy-responsive states.

Collectively, emerging evidence suggests that p53 should be viewed not only as a tumour suppressor controlling cell-intrinsic stress responses, but also as a central regulator of the hepatic tumour ecosystem. Through its influence on inflammatory signalling, immune surveillance, stromal activation, and metabolic pathways, p53 signalling can influence multiple components of the HCC tumour microenvironment. Consequently, disruption of p53 function may promote tumour progression not only through loss of tumour cell control, but also through establishment of an immunosuppressive microenvironment. Understanding these broader roles of p53 in shaping the HCC TME may unlock new therapeutic opportunities. Future advances will likely depend on integrating genomic stratification based on *TP53* status with therapies designed to modulate tumour immunity and reshape the TME, ultimately enabling more precise and effective, and gentler treatments for patients.

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Abbreviations

The following abbreviations are used in this manuscript:

AFB1	Aflatoxin B1
α-SMA	Alpha-smooth muscle actin
ATM	Ataxia-telangiectasia mutated
ATR	Ataxia-telangiectasia Rad3-related
CAF	Cancer-associated fibroblasts
CDK	Cyclin-dependent kinase
CTD	C-terminal regulatory domain
CTLA-4	Cytotoxic T lymphocyte associated protein 4
DBD	DNA binding domain
DDR	DNA damage response
ECM	Extracellular matrix
EMT	Epithelial mesenchymal transition
FGF	Fibroblast growth factor
GOF	Gain of function
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HGF	Hepatocyte growth factor
HPD	Hyper progressive disease
HSC	Hepatic stellate cells
ICI	Immune checkpoint inhibitors
IFN-γ	Interferon gamma
IRF1	Interferon-regulatory factor 1
JAK	Janus kinase
LOF	Loss of function
MASH	Metabolic dysfunction-associated steatohepatitis
MASLD	Metabolic dysfunction-associated steatotic liver disease
Mdm2	Mouse double minute 2
MdmX (Mdm4)	Mouse double minute 4
MDSC	Myeloid-derived suppressor cells
mTOR	Mammalian target of rapamycin
NAFLD	Non-alcoholic fatty liver disease
NF-κB	Nuclear factor kappa-light chain-enhancer of activated B cells
NK cell	Natural killer cell
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PRD	Proline-rich domain
Rb	Retinoblastoma protein
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SASP	Senescence-associated secretory phenotype
STAT3	Signal transducer and activator of transcription 3
SV40	Simian vacuolating virus 40
TAD	Transactivation domain
TET	Tetramerization domain
TGF-β	Transforming growth factor-beta
TMB	Tumour mutational burden
TME	Tumour microenvironment
Treg	Regulatory T cell
WIP1	Wild-type p53-induced phosphatase 1
Wt	Wild-type

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