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REVIEW

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Harnessing p53 for targeted cancer therapy: new advances and future directions

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ABSTRACT

The transcription factor p53 is the most frequently impaired tumor suppressor in human cancers. In response to various stress stimuli, p53 activates transcription of genes that mediate its tumor-suppressive functions. Distinctive characteristics of p53 outlined here enable a well-defined program of genes involved in cell cycle arrest, apoptosis, senescence, differentiation, metabolism, autophagy, DNA repair, anti-viral response, and anti-metastatic functions, as well as facilitating autoregulation within the p53 network. This versatile, anti-cancer network governed chiefly by a single protein represents an immense opportunity for targeted cancer treatment, since about half of human tumors retain unmutated p53. During the last two decades, numerous compounds have been developed to block the interaction of p53 with the main negative regulator MDM2. However, small molecule inhibitors of MDM2 only induce a therapeutically desirable apoptotic response in a limited number of cancer types. Moreover, clinical trials of the MDM2 inhibitors as monotherapies have not met expectations and have revealed hematological toxicity as a characteristic adverse effect across this drug class. Currently, combination treatments are the leading strategy for enhancing efficacy and reducing adverse effects of MDM2 inhibitors. This review summarizes efforts to identify and test therapeutics that work synergistically with MDM2 inhibitors. Two main types of drugs have emerged among compounds used in the following combination treatments: first, modulators of the p53-regulated transcriptome (including chromatin modifiers), translatome, and proteome, and second, drugs targeting the downstream pathways such as apoptosis, cell cycle arrest, DNA repair, metabolic stress response, immune response, ferroptosis, and growth factor signaling. Here, we review the current literature in this field, while also highlighting overarching principles that could guide target selection in future combination treatments.

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Introduction

TP53 is the most frequently mutated tumor suppressor gene in cancers. In The Cancer Genome Atlas (TCGA) collection [1], *TP53* mutations range from 1% to 5% in papillary thyroid carcinomas, renal clear cell carcinomas, renal papillary cell carcinomas, and cervical squamous cell carcinomas. Conversely, mutation rates reach up to 70–95% in head and neck squamous cell carcinomas, lung squamous cell carcinomas, and ovarian serous cystadenocarcinomas. *TP53* mutation rates are significantly increased in 15 out of 18 tested cancer types. When normalized on the tumor type prevalence, *TP53* is mutated in approximately 36% of all cancer cases [2]. In tumors that retain the wild-type variant of the gene, the p53 network is often inactivated through alternative mechanisms, including viral oncoproteins or by overexpression of negative regulators. The varying frequencies of *TP53* mutations across different cancer types serve as an important benchmark for understanding p53's role in tumor suppression. Therefore, i) *TP53* mutations provide tumors with a fitness advantage that surpasses all other tumor suppressor gene mutations. ii) Since *TP53* mutations occur in almost all cancer types, the affected mechanisms must be numerous or common to all these tissue types. Research has revealed that both are true. iii) The wide range of *TP53* mutation frequencies across different cancer types suggests a tissue-specific impact of the *TP53*-encoded

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transcription factor (TF) p53 on carcinogenesis and/or tissue-specific mechanisms for disabling p53. Taken together, patients are likely to benefit more from restoring p53 activity in tumors than from reactivating any other tumor-suppressive mechanism. Therapies based on p53 activation are expected to be effective across different tumor types, yet only if differences in context are addressed. Since several other genetic and epigenetic alterations need to accumulate for cancer development [3,4], monotherapies relying solely on p53 activation are likely to fail. Moreover, targeting just one tumor-promoting event at a time often leads to resistance development and increased mortality [5–7]. Essentially, p53 represents a powerful target for cancer treatment among tumor suppressors and a prime candidate for combination therapy (polytherapy).

Unique features of p53

Among transcription factors (TFs), p53 stands out with its consistent set of binding sites, a hallmark that significantly influences p53 biology. In a study comparing TF binding sites in two cancer cell lines – HCT116 (colon carcinoma) and MCF7 (breast carcinoma) – it was found that while p53 occupancy overlapped by 48%, the common binding sites for other TFs such as ELF1, EGR1, TEAD4, JUND, SIN3A, and CEBPB ranged from 3.3% to 12.5% [2,8]. Further meta-analyses of p53 chromatin immunoprecipitation-sequencing (ChIP-seq) data identified over 1000 common binding sites present in at least 20 out of 41 studies [9,10]. This distinct binding pattern can be attributed to the specific manner in which p53 interacts with target loci. Since p53 binds DNA as a self-assembled tetramer with all four molecules interacting with the consensus sequence [11], the resulting binding motif is about 20 base pairs long [2,12,13]. This is substantially longer than the motifs for more than 98% of other transcription factors, which typically range from 7 to 15 base pairs [14] with a median of 10 base pairs [15]. A consistent set of binding sites thus allows for the induction of a signature gene set necessary for characteristic phenotypical responses.

Opening compacted heterochromatin for transcription is crucial not only for cell development but also for executing various cellular programs, including stress responses [16,17]. More than 20 years ago, Espinosa and Emerson [18] demonstrated that p53 binds nucleosomal DNA. Since then, growing evidence has portrayed p53 as a “pioneer” TF on a genome-wide scale [19–22], able of binding to condensed chromatin and initiating transcription, further contributing to a relatively steady character of the p53-regulated transcriptome.

Unlike its family members *TP63* and *TP73*, *TP53* mRNA is expressed in virtually all tissue types [1]. Given that p53 activation relies on halted degradation of the protein produced at a sustained rate, the widespread p53 mRNA expression facilitates p53 pathway activation in nearly every cell type.

Basically, the tumor-suppressive capacity of p53 is ensured by three key features: First, its binding sites are defined by a relatively strict and long binding motif. Second, its dependency on chromatin status is mitigated by its pioneering function. Finally, *TP53* mRNA expression is universal.

Diverse stress signals activate p53

Numerous stress stimuli associated with tumor promotion or progression induce p53 (Figure 1). A crucial regulator of p53 activity is MDM2 (Mouse Double Minute 2) [23,24], an E3 ubiquitin ligase that tags oligomerized p53 molecules for proteasomal degradation [25–28]. The *MDM2* gene is a transcriptional target of p53, forming a tight negative feedback loop [29]. This loop, combined with the short half-life of the p53 molecule (5–20 min) [30], enables rapid induction of the p53 network. MDM2 works alongside the homologous protein MDM4 (also known as MDMX or HDMX), which is a prominent negative regulator of p53’s transcriptional activity [31] although lacking a functional E3 ligase domain. Mouse embryos missing either MDM2 or MDM4 exhibit embryonic lethality, which can be fully rescued by *TP53* knockout [32–36].

Unlike *MDM2*, *MDM4* is not transcriptionally induced by p53 and is primarily regulated at the protein level through phosphorylation by kinases such as ATM, CHK2, and CK1, by MDM2-mediated ubiquitination, or interaction with stabilizing partners like FAM193A [37,38].

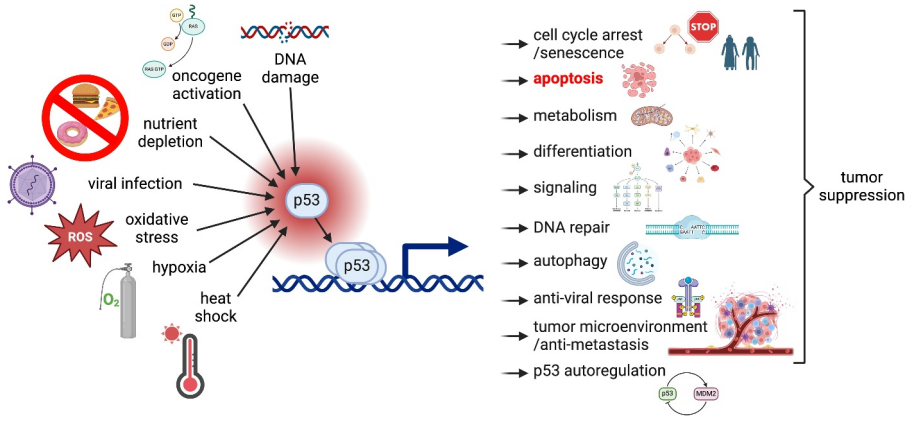

Figure 1. Stimuli inducing p53 and cellular programs impacted by p53 activation.

Stress signals activating p53 are transduced by various upstream regulatory molecules that connect sensors to p53 as a stress response hub. Mechanisms leading to p53 stabilization are partially specific to different types of stress. For instance, DNA damage-induced p53 activation involves kinases ATM, ATR, DNA-PK, CHK1, and CHK2 [39–43]. Other kinases like JNK and p38 contribute to p53 induction in response to oxidative or mechanical stress [44,45]. Upon stress signaling, activated kinases phosphorylate specific residues on p53, MDM2, MDM4, and other associated proteins to release p53 from complexes, increase its protein levels, and enable target gene transactivation.

A crucial role of activating kinases in the process of p53 induction is balanced by the phosphatase activity of WIP1/PPM1D (Wild-type p53-Induced Phosphatase 1) [46–50]. Like MDM2, WIP1/PPM1D is a direct transcriptional target of p53 [2,51] forming another negative feedback loop regulating the activity of the p53 network. However, WIP1/PPM1D plays a less prominent role in repressing p53 than MDM2, as inhibiting WIP1/PPM1D alone is insufficient for p53 activation [52] and unlike MDM2/MDM4 knock-outs, WIP1/PPM1D-null mice are viable [53]. Other regulatory feedback loops impacting p53 activity involve cyclin G [54], PTEN/AKT, and SIAH-1/beta-catenin/ARF [55].

Overall, approximately 45 amino acids in the p53 molecule can undergo modifications such as phosphorylation, methylation, acetylation, sumoylation, ubiquitination, and other post-translational modifications. As deciphering the full implications of these alterations is beyond the scope of this text, readers are encouraged to consult more detailed reviews on this topic [56–60].

Other stimuli that induce p53 (Figure 1), such as oncogene activation, utilize the tumor suppressor ARF, which directly interacts with the MDM2 molecule to block p53 degradation [61,62]. The mechanism of p53 activation by starvation involves multiple pathways, including AMPK (AMP-activated protein kinase) [63–65] and mTOR (mammalian Target Of Rapamycin) kinase [66,67]. Additionally, p53 phosphorylation by IKKβ kinase in response to glutamine deprivation represents another mode of activation in nutrient-deprived cells [68]. In melanoma and breast cancer cells, starvation leads to the dissociation of the inhibitory protein REV1 from its complex with p53 ok [69]. The exact mechanism by which hypoxia activates p53 is unclear and likely depends on oxygen concentration and hypoxia duration [67]. Both hypoxia and p53 networks share numerous genes with regulatory functions that facilitate crosstalk between these networks [2,70,71]. Notably, MDM2 inhibitors retain efficacy under hypoxic conditions [72] that are associated with therapy resistance [73] and common to solid tumors as small as 1 mm in diameter [74].

p53 activity regulation by viral infection was first illustrated by its discovery as a molecule co-precipitating with the large T-antigen of the SV40 virus [75–79]. While many direct interactions of

p53 with viral proteins inhibit its activity (e.g., human papillomavirus protein E6) [80,81] other viral proteins can induce a p53 response (e.g., West Nile virus capsid protein) [82], and HIV-1 Tat and Vif proteins [83–85]. Indirect mechanisms, such as interferon-stimulated phosphorylation of p53 by ATM kinase [86] and upregulated *TP53* mRNA transcription [86,87] may represent more general responses to viral infection.

Corrupted regulatory mechanisms silence wild-type p53 in cancer

Aberrant activity of upstream regulators mutes the p53 network, representing a crucial step in carcinogenesis for tumors with wild-type *TP53*. The oncogene *MDM2* is overexpressed in various cancers, including sarcomas and breast, lung, and colon cancers [88,89] primarily due to gene amplification. Single nucleotide polymorphisms in the *MDM2* promoter can also increase expression and enhance cancer risk [90,91]. Similarly, the *MDM4* oncogene is frequently amplified and overexpressed across many cancers [92], although other types of *MDM4* mutations are rare [93]. Amplifications of the *PPM1D* oncogene have been reported in several cancers [94] including 11% of primary breast tumors [49,95] leukemia [94], and ovarian cancer [96,97]. Truncating gain-of-function mutations result in constitutively active PPM1D/WIP1 phosphatase resistant to degradation signals [98,99], conferring chemotherapy resistance [100] and accelerated tumor growth in mouse models [101,102]. *PPM1D* mutations occur at increased frequency in a variety of tumor types [103] and are mutually exclusive with *TP53* mutations [2,98].

Overall, p53 upstream negative regulators are prime targets for a broad range of inhibitors that can reactivate the p53 network.

A group of canonical p53 target genes defines principal functions of the p53 network

Activated p53 stimulates transcription of a complex network of target genes involved in various tumor-suppressive programs [78]. Notwithstanding tissue-, treatment-, or signal-specific outcomes of p53 activation, a distinct group of genes under direct control of p53 serves as a signature of its activity [2,9,104,105]. Thus, p53 acts as an integrating node responding to diverse signals through transactivation of a well-defined network of canonical target genes. Understanding the function of such genes is crucial for insight into the entire network's role in tumor suppression. By combining experimental approaches [2,106] and extensive meta-analyses [9,104] we refined our previous attempt to identify canonical p53 target genes (Figure 2, Supplementary Table S1). Assigning functions to these 105 protein-coding genes illustrated that most have tumor-suppressive roles as mediators of cell cycle arrest, apoptosis, senescence, differentiation, metabolism, autophagy, DNA repair, signaling, anti-viral response, and anti-metastatic functions. Autoregulation represents another staple within the p53 network. Contrasting with other roles of p53, about 17% of canonical targets may serve ambiguous or tumor-promoting functions labeled as "survival/proliferation" (Figure 2). However, gene characteristics are frequently obtained from cellular systems with unknown p53 network status which could impact the net effect of individual gene activity. Many p53 target genes exhibit multiple or context-dependent functions, which adds complexity to analyzing the p53 network's overall functionality.

Tumor-suppressive power of p53 is distributed throughout the network

Tumor suppression by individual genes may be rated by mutation occurrence in tumor samples or by studies utilizing genetically modified experimental animals. In line with previous reports, only a few canonical p53 target genes are significantly mutated in tumors [2] (*FBXW7*, *CDKN1A*, *TP53INP1*, *PPM1D*, and *NOTCH1, rev. by Indeglia and Murphy* [107], with low mutation frequency (0.4–3.5%)[2] compared to a *TP53* mutation rate of 36.1%. Moreover, *CDKN1A*, *FBXW7*, and *NOTCH1* are significantly mutated in both *TP53* wild-type and mutant tumors suggesting p53-independent roles of the genes in carcinogenesis [2]. Tumor suppression studied in a *TP53*-null mouse model documented spontaneous

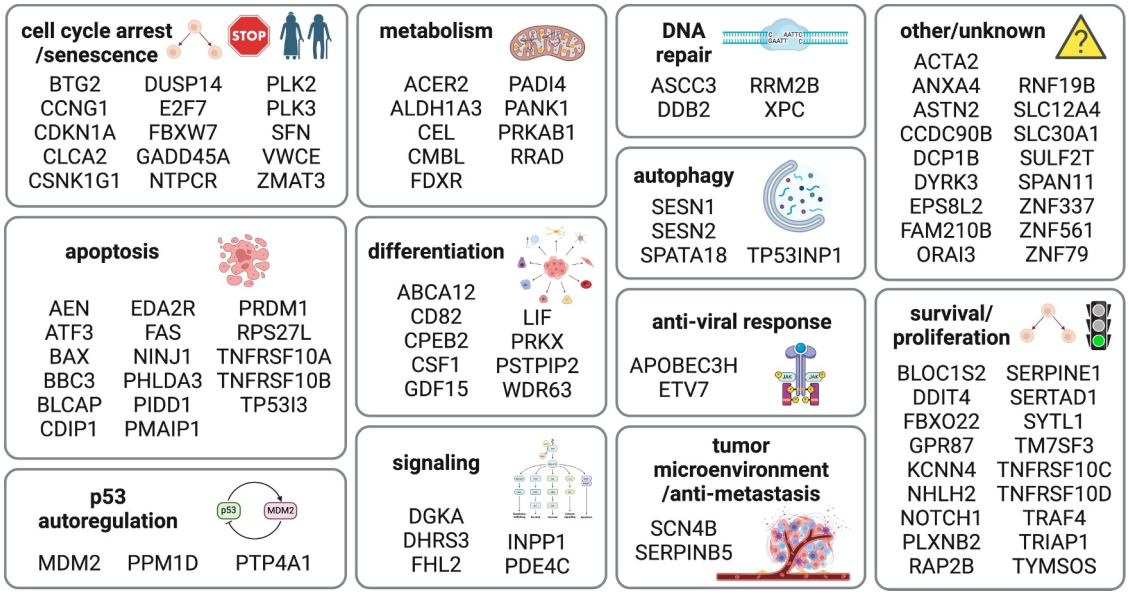

Figure 2. Canonical p53 network genes. Genes were associated with a specific function based on current literature. Frequently, genes are involved in multiple cellular programs and authors used their best judgment to assign a gene with the prevailing role in the p53 response.

development of various tumors early on, while mice lacking specific p53 target genes seldom exhibited increased tumor development without additional stressors. Depending on mouse strain, *TP53*-null mice develop a spectrum of tumors and lymphomas between 6 [108,109] and 10 months [110,111]. Conversely, mice lacking *CDKN1A* show no increase in chromosomal instability or cancer formation [112]. However, an extra copy of the gene protects experimental animals from chemically or oncogene-induced cancer [113]. Loss of BBC3/PUMA is insufficient to predispose mice to spontaneous tumor development alone [114] only if mice are exposed to carcinogens or of tumor-prone background [115,116]. Similarly, mice lacking *GADD45* [117], *GDF15* [118], *PLK3* [119], *BTG2* [120], *FAS* [121], *BAX*, *BAK*, or *BAX/BAK* double knock-outs [122,123] do not develop spontaneous tumors. Triple knock-out of *ZMAT3*, *BBC3/PUMA*, and *CDKN1A* causes spontaneous tumor development in ~50% mice aged over 460 days [124]. The same mouse strain lacking *TP53* displayed much earlier tumor occurrence with no animals surviving over 250 days [124]. Interestingly, mice depleted of ATF3 show increased incidence of cancer compared to wild-type strain (24% vs. 69%), although at a relatively high age ~2 years [125]. Finally, DDB2-null mice also develop spontaneous tumors at 20–25 months and are more sensitive to UV-induced skin cancer [126].

These findings illustrate that no single p53 target mediates a majority of anti-tumor functions, and tumor-suppressive capacity is distributed across many genes within the network [2]. Therefore, drugs activating p53 should provide greater benefits in cancer treatment than individual p53 target induction.

Activation of p53 in cancer treatment

Irradiation and numerous chemotherapy agents induce p53 expression in *TP53* wild-type tumors [127–130] (Figure 3). Importantly, chemotherapy is more effective in *TP53* wild-type tumors [128,131–133], and a loss of functional p53 in tumor development is associated with worsened prognosis and shorter survival of the patient [134–141]. These findings, along with mechanistic studies exploring the role of p53 in EMT and MET [142,143] suggest that p53 is not only a potent suppressor in the initiation phase of carcinogenesis, but also in tumor progression and metastasis. Therefore, more than 50% of cancer patients

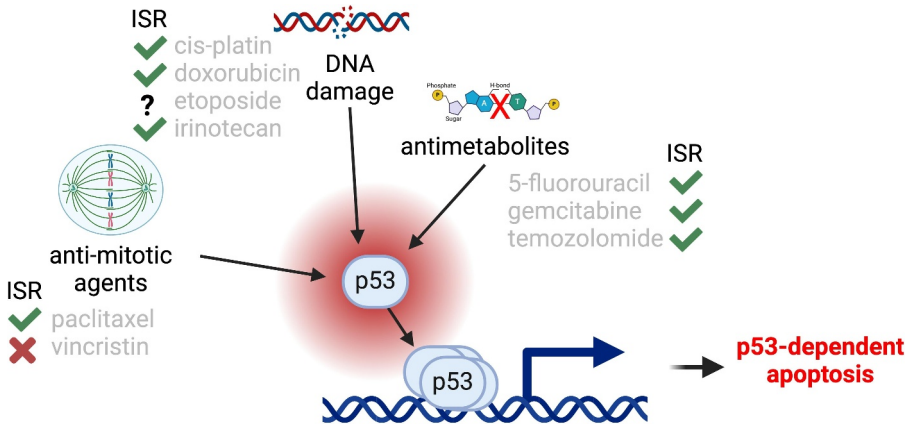

Figure 3. Numerous chemotherapeutics activating p53 also induce the integrated stress response (ISR).

retaining wild-type *TP53* may benefit from treatments based on targeted activation of the p53 network including cases of advanced and disseminated disease since wild-type *TP53* is retained in a major fraction of metastatic tumors in colorectal cancer (45% of Dukes' D stage) [144–146] breast (70% of HR+, 56% of invasive ductal carcinomas) [147], lung (78% of NSCLC lymph node metastases) [148], or prostate (70%) [149].

Traditional chemotherapy is associated with substantial side effects including gene mutation in non-cancerous cells [150] and secondary cancer development [151–155]. Targeted therapies based on inactivation of specific oncogenes and induction of tumor-suppressive mechanisms are designed to avoid most of the negative outcomes of chemotherapy [156,157]. Highlighting general consensus on the importance of p53 in cancer biology, many small molecule inhibitors were developed to harness the tumor suppressive capacity of the p53 network for targeted anti-tumor therapy [158–160]. By far, the greatest number of drugs designed to induce the p53 network is aimed at disrupting the interaction between p53 and MDM2. First compounds of this class were nutlins [161], discovered by a team of scientists from Roche, and named after Nutley, New Jersey [162]. Nutlins trigger p53 accumulation in the *TP53* wild-type cell lines, induce p53 target genes, cell cycle arrest, and apoptosis *in vitro* and xenograft tumor growth arrest *in vivo* [161]. However, the prevailing apoptotic responses *in vitro* and xenograft tumor growth suppression are limited to a minority of sensitive cell lines, as the typical response to the most potent analog Nutlin-3a (referred to as nutlin) is a cell cycle arrest [163,164]. Variable levels of cell death via apoptosis triggered by MDM2 inhibition were reported in leukemia in general [165,166], lymphoma [165,167–171], multiple myeloma [172,173], melanoma [165], neuroblastoma [165,174], glioblastoma [175], mesothelioma [165], gastric cancer [176], renal cancer [165], testicular carcinoma [177], osteosarcoma [163], and Ewing sarcoma [178,179]. Unfortunately, most of the studies document *in vitro* observations without corresponding *in vivo* experiments, since the latter frequently fail recapitulating fully promising anticancer effects reported from tissue cultures [171,180].

Overall, MDM2 inhibition activates p53 but does not lead to strong apoptotic response *in vitro* in most of the tumor types. In selected cancers with high sensitivity to MDM2 inhibitors, clinical trials [181] demonstrated only moderate results when used in monotherapy, further complicated by p53 induction in bone marrow leading to thrombocytopenia and neutropenia [182–184]. Recently, clinical trials of ALRN-6924 (Sulanemadlin), a first-in-class, stabilized, cell-permeable peptide-binding MDM2 and MDM4 [185] were terminated owing to severe grade 4 neutropenia and alopecia, failing to meet the main endpoints of the trial (NCT05622058) [186,187]. Neutropenia and thrombocytopenia were reported for most if not all clinically tested

MDM2 inhibitors including RG7112 (RO5045337) [188], idasanutlin (RG7388, RO5503781) [189], milademetan (DS-3032b, RAIN-32) [190], HDM201 (siremadlin, NVP-HDM201) [191], CGM097 (NVP-CGM097) [192], APG-115 (alrizomadlin) [193], KRT-232 (AMG-232, navtemadlin) [194,195], BI-907828 (brigimadlin) [196], MK-8242 (SCH 900,242) [197], and SAR405838 (MI-77301) [184,198,199]. Altogether, myelosuppression and gastrointestinal toxicity have been identified as class effects of the MDM2 inhibitors [200]. To enhance treatment efficacy and minimize patient side effects, multiple strategies were implemented for optimizing MDM2 inhibitor therapy:

(1) Intermittent dosing: A phase-1 clinical trial of the MDM2 inhibitor milademetan demonstrated that intermittent dosing reduced hematological adverse effects while maintaining efficacy [201].
(2) Novel targeted approaches: New methods for targeted p53 induction are being explored, including small molecule degraders of MDM2 based on proteolysis targeting chimera (PROTAC). These have shown effectiveness at low nanomolar doses without toxicity in mouse models [183,202]. However, the overall low toxicity of PROTACs [203] still needs confirmation in clinical trials for degraders targeting MDM2 [204].
(3) Combination therapies: MDM2 inhibitors are being used in combination with both chemotherapy and other targeted drugs. This approach aims to improve existing treatment protocols or develop novel strategies based on our understanding of tumor-specific processes and cancer tissue vulnerabilities. The validity of this approach is underscored by significant improvements in patient outcomes such as doubling the number of patients with advanced biliary tract cancer responding to treatment and doubling the remission rate in AML patients using MDM2 inhibitor combination therapy instead of monotherapy [205,206]. Currently, combination therapy constitutes the main line in (pre-)clinical research toward cancer treatments based on targeted induction of p53.
(4) Drug delivery systems: While not yet fully explored in the MDM2 inhibitor field, recent successful use of the drug nanoencapsulation [207] shows promise for overcoming hematological toxicity and is likely to inspire future research in this direction.

Boosting the apoptotic response to p53 activation by combination treatment

Combination therapy, which uses two or more different types of therapy, is fundamental to cancer treatment [208]. Combination therapies not only better address the nature of the disease – they also produce a more effective treatment response in fewer cycles, reduce adverse effects of the therapy, and limit incidence of resistance [208–210]. Activation of the p53 network by MDM2 inhibitors is being explored to improve the outcome of traditional chemotherapy and radiotherapy along with targeted polytherapy. Possible synergy between p53 network induction and immunotherapy is also being investigated, since p53 both directly and indirectly controls elements implicated in immune response [211].

MDM2 inhibitors in combination with chemotherapy or irradiation

In malignant tissues, dampening of upstream signaling required for p53 induction restrains tumor suppressive capacity of the p53 network [212,213]. Since many chemotherapeutics cause DNA damage and p53 activation is required for full treatment response, such disruption in signaling negatively impacts treatment efficiency. MDM2 inhibitors are therefore tested in combination with chemotherapy and irradiation to improve the therapeutical treatment outcome in a variety of cancer types. Gastric cancer cell lines treated with 5-fluorouracil (5FU) or cisplatin in combination with nutlin displayed increased apoptosis *in vitro* and xenograft tumor growth arrest [176]. Nutlin also increased cytotoxicity of doxorubicin and bortezomide in cutaneous T cell lymphoma cells [167,171], renal cell carcinomas [168], and hepatocellular carcinomas [214]. Similarly, nutlin augmented anti-proliferative and pro-apoptotic

effects of etoposide and cisplatin in neuroblastoma [215] and testicular carcinoma [177]. Furthermore, nutlin increased sensitivity of multiple tumor types to irradiation both *in vitro* and *in vivo* [216–218].

In a reversed strategy, MDM2 inhibitors were employed to protect *TP53* wild-type cells in healthy tissue via cell cycle arrest while proliferating *TP53* mutant tumor tissue is targeted by taxol [219] or S-phase-specific chemotherapy [220–222].

Essentially, clinical trial results using MDM2 inhibitors and chemotherapy have not yet fulfilled expectations. Among patients with relapsed/refractory acute myeloid leukemia, MDM2 inhibitor idasanutlin [189] in combination with cytarabine improved overall response rate, yet failed to significantly enhance rates of overall survival or complete remission [223]. These discouraging results suggest that lack of p53 activation, which may be remedied by MDM2 inhibitors, is not the main reason for chemotherapy failures. Besides *TP53* mutations, resistance to chemotherapy and MDM2 inhibitors may be mediated by identical mechanisms [224,225] including activation of ABC transporter P-glycoprotein [226]. Altogether, combinations of MDM2 inhibitors with chemotherapy may boost p53-dependent responses, although dependence on the same effector represents a weakness of such approach.

Combination targeted therapy employing MDM2 inhibitors

Mutational profiling of tumors offers an essential insight into cancer biology, which is critical for designing efficient treatment strategies. Sporadic cancer cells contain thousands of genomic alterations [227] including a handful [228] involving biologically relevant genes governing cell proliferation and required for metastatic spreading. The average number of four driver mutations per tumor [228] illustrates disease complexity and explains why clinical benefits of targeted monotherapies are almost always limited [229,230]. Over the past 15 years, the proportion of monotherapies in clinical trials has declined from 70% to 20–30% [229].

A mixture of compounds with distinct aims (polytherapy, multi-node targeting) widens the therapeutic window and addresses the two main drawbacks of targeted cancer therapy: resistance development and adverse effects [209,230]. Such an approach has also been adopted to p53-centric treatments employing MDM2 inhibitors. So far, none of the proposed avenues have reached the regulatory approval for cancer treatment. Nevertheless, these obstacles could be potentially overcome with two types of drugs and biomolecules synergizing with MDM2 inhibitors (Figure 4):

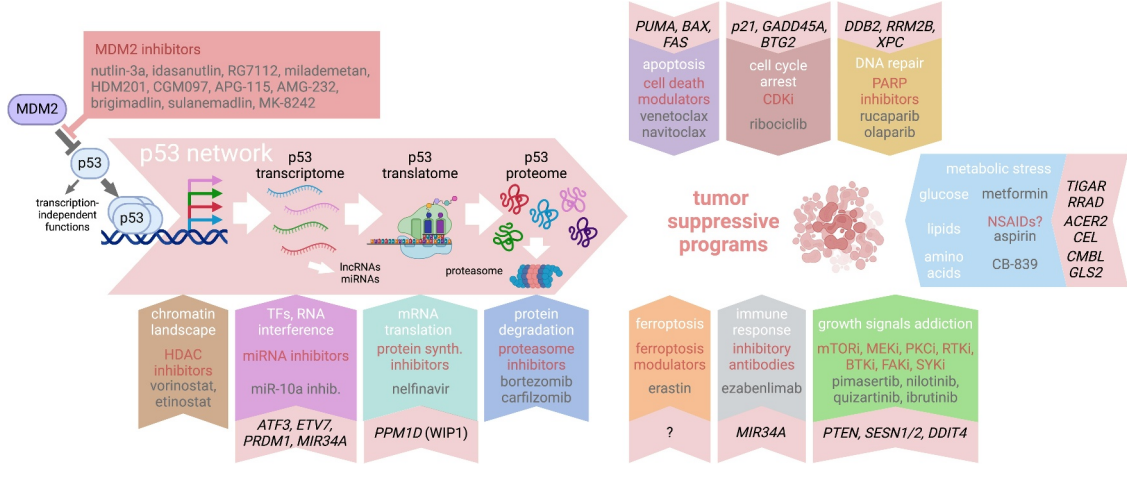

Figure 4. Two groups of drugs synergizing with MDM2 inhibitors. On the left are compounds targeting p53 network at various regulatory levels, on the right are therapeutics which modulate carcinogenesis-relevant processes and tumor survival such as apoptosis, cell cycle arrest, DNA repair, metabolism, ferroptosis, tumor immune response, and addiction to growth signals. Genes in italics are p53 targets.

(1) Compounds targeting the entire p53 network by changing chromatin landscape and/or altering the p53-dependent transcriptome, translatome, and proteome.
(2) Drugs which modulate processes relevant to carcinogenesis and tumor survival such as apoptosis, cell cycle arrest, DNA repair, metabolism, ferroptosis, tumor immune response, and growth factor signaling.

Chromatin accessibility

Histone deacetylases (HDACs) and DNA methyl transferases (DNMTs) remodel chromatin landscape and change gene transcription [231,232] including *TP53* [233] and p53 target genes [234–236. p53 activity affecting transcription regulation by HDACs and DNMTs [237] seems to be principally regulated by direct interactions with DNMT [235,238] and HDAC [239,240] complexes, as transcriptional regulation of participating factors like SLC43A2 [237,241] by p53 is not common [2,52,104].

Several inhibitors of HDACs have been approved by the FDA for the treatment of hematological malignancies, however results in solid tumors including tumor growth promotion are mixed [242,243]. One explored strategy for HDAC inhibitor use for solid tumor treatment is combination with targeted therapeutics including MDM2 inhibitors. In p53 wild-type lines derived from solid tumors, MDM2 inhibitors synergized with HDAC inhibitors vorinostat (suberoylanilide hydroxamic acid, SAHA) [244], sodium butyrate, entinostat (MS-275) [245], and apicidin [246] to induce apoptosis [247]. Combination of HDAC inhibitor entinostat and idasanutlin synergized *in vitro* to induce apoptotic response in colorectal carcinoma cell lines [207]. Interestingly, with this study, Abed and coauthors used nanoparticles for co-capsulation of both drugs, demonstrating both efficiency *in vitro* and curbed hematological toxicity in a mouse model. Nonetheless, synergistic effects of nutlin and HDAC inhibitor valproic acid have also been reported in AML both *in vitro* and *in vivo* [248].

Crosstalk between p53 signaling and HDAC-regulated gene networks is context-dependent, since both p53 induction [249] and downregulation of p53-driven transactivation by HDAC inhibitors [250] were chronicled. Moreover, decrease in HDACs expression upon MDM2 inhibition [251,252] is a plausible mechanism for exacerbated anti-proliferative effects of joint inhibition of both pathways, justifying the development of compounds with dual specificity toward MDM2 and HDAC [253].

Modulation of the p53 transcriptome

The p53 transcriptome is influenced by several mechanisms [10,254] such as regulation of transcriptional activity, mRNA splicing, transport, and stability. Possibilities of direct therapeutical modulations of cancer cell transcriptomes to improve efficiency of MDM2 inhibitors are limited by availability of specific drugs designed for *in vivo* use [255]. Notable exceptions are represented by ligand-activated nuclear receptors for androgen (AR) and estrogen (ER) which are targeted in hormone-driven prostate or breast cancers. However, combinations of MDM2 inhibitor with androgen therapy are complicated by MDM2-dependent degradation of AR [256] with opposing effects on critical prostate cancer cell subpopulations. First, in a majority of AR-positive cells, MDM2 facilitates ubiquitination and proteolysis of the AR [257], and MDM2 inhibition leads to AR upregulation, increased transactivation of AR-target genes [258], and protection from apoptosis induced by the anti-androgen hydroxyflutamide [259]. Conversely, MDM2 promotes proliferation and survival in AR-negative prostate cancer stem cells, while MDM2 inhibitors induce cell death [260].

In breast cancer cells, ER activity accelerates proliferation of breast cancer cells and anti-estrogens or aromatase inhibitors have been used in monotherapy for many years. Yet, variable efficacy and resistance development inspired the development of combination targeted therapies [261] with inhibitors of mTOR, PI3K, CDKs, and PD-1/PD-L1. Efficiency of a combined treatment of anti-estrogens and MDM2 inhibitors is hampered by direct binding of ER to the p53 molecule and transactivation inhibition [262]. Estrogen degraders like fulvestrant (Faslodex) [263]

potentiate MDM2-induced senescence and tumor growth deceleration *in vivo* [264].

Other mechanistic studies document how modulation of transcription co-regulators may potentiate therapeutically desirable phenotypes initiated by p53 induction. Inhibition of the transcription factor NFkB by caffeic acid phenyl ester (CAPE) [265] moderately increased cell death response to nutlin treatment in Ewing sarcoma models [178].

Overall, transcriptome modulations by targeting TFs to increase the efficiency of MDM2 inhibitors are hampered either by lack of pharmacological tools, weak effects of drug combinations, antagonistic interactions between networks, or heterogeneity in tumor population response. Notwithstanding, the greatest obstacle likely resides in the function of the MDM2i-synergizing TF modulator. If the presumed outcome of the synergizing drugs is greater transactivation of p53 target genes resulting in stronger apoptotic response in cancer cells, a TF activator or stabilizer may be needed. Regrettably, designing an activator seems to be challenging, as illustrated by the fact that between 2018 and 2022, the FDA approved 50 new TF inhibitors and only two activators [266]. Therefore, novel approaches including synthetic on-demand TFs [267] may be needed for progress in this line of research.

MicroRNAs (miRNAs) are small non-coding RNAs which regulate gene expression by either facilitating mRNA degradation or inhibiting translation [268]. In carcinogenesis, miRNAs act both as oncogenes and tumor suppressors [269]. Numerous miRNAs are directly induced by p53, including tumor suppressor miR-34a targeting anti-apoptotic genes, cyclins, CDKs, anti-senescence genes, and mediators of epithelial–mesenchymal transition (EMT) [270]. Other miRNAs upregulated by p53, such as miR-145, miR-107, miR-192, and miR-215, also target cell cycle and proliferation genes, anti-apoptotic regulators, pro-invasion factors, and oncogenes [271–275], albeit at instances when tumor-promoting roles for miRNAs activated by p53 were reported [276], illustrating prevalent context dependency in miRNA-mediated gene regulation [277]. Furthermore, certain p53-induced miRNAs including miR-34a and miR-215 target the *TP53* mRNA creating negative feedback regulatory loops [278].

Advances in RNA therapeutics development and the global success of SARS-CoV-2 mRNA vaccines have increased the interest in RNA-based therapies including cancer treatment [279]. Key advantages of miRNAs and other RNA-interference techniques are adaptability, modularity, stability, and potential use in combination therapy [280]. RNA-based cancer therapeutics, including RNA interference, represent an opportunity for a major technological leap in targeted therapy owing to unprecedented freedom regarding target choice, low cost, speedy, and easy-to-automate preparation, as well as virtually limitless possibilities for combination treatments and variable half-life of the molecule. However, despite recently renewed attention to RNA therapeutics, no miRNA-based treatments were approved by the FDA as of early 2024, and few pre-clinical works explored possible combinations with MDM2 inhibitors.

Oncogenic miR-10a overexpressed in AML models [281] modulates the antiproliferative effects of nutlin. Interestingly, an miR-10a inhibitor inverted cellular response to nutlin by attenuating cell cycle arrest response while increasing apoptosis. Synergistic effects of miR-10a and MDM2 inhibitors were demonstrated both *in vitro* and *in vivo* [282].

In the near future, we should expect substantial advances in the field of RNA-based cancer therapeutics. The potential for combining these approaches with MDM2 inhibitors could open new avenues for more effective and personalized cancer treatments.

mRNA translation as a key regulatory step for the outcome of p53 activation

Enhancing expression of the pro-apoptotic genes is an obvious strategy for cell death induction in cancer cells treated with MDM2 inhibitors [283]. Since targeting individual genes in a group with a high level of redundancy [284] is impractical, compounds with broader impact, yet highly specific, seem to be a better choice as illustrated by BH3 mimetics [285]. Recently, we presented such strategy for selective regulation of genes in the p53

network to elicit strong apoptotic response [52]. We subsequently discovered a negative regulatory feedback loop within the p53 pathway with a capacity to downregulate expression of network genes including pro-apoptotic Puma, Fas, and Bax, which can be disrupted pharmacologically and instigate cell death in combination with MDM2 inhibitors [52].

Activation of p53 by MDM2 inhibitors leads to direct transactivation of the PPM1D gene and increased expression of the PPM1D phosphatase, which in turn maintains eukaryotic translation initiation factor eIF2α in an active state, preventing a switch to an alternate translation mechanism favoring mRNAs of stress response genes. Disrupting this negative feedback loop by inhibition of either PPM1D or the downstream eIF2α impacts the p53 network at two different levels: First, eIF2α inhibition is associated with increased translation of TF ATF4, which amplifies p53-driven gene transactivation. Second, mRNAs of multiple pro-apoptotic p53 target genes are preferentially translated. This series of events results in reinforced cell cycle arrest response and robust apoptosis [52].

Intriguingly, numerous p53-activating chemotherapeutics also induce ISR [286–289] (Figure 3). As expected, active eIF2α prevented apoptosis in cancer cells treated with doxorubicin [290]. Therefore, eIF2α inhibition by nelfinavir [291], guanabenz, salubrinal [292], and (ONC201/TIC10) may be used to increase the apoptotic response to chemotherapy [293,294] or radiotherapy [295]. Notably, in a *TP53* mutant colorectal carcinoma cell line HT29, ISR induction by ONC201 failed to synergize with chemotherapeutics like irinotecan, oxaliplatin, and 5-FU [296].

Generally, cancer cells are addicted to a high rate of translation [297] and exhibit increased levels of eIF2α phosphorylation/ISR compared to normal cells [298–301] as a likely outcome of various types of stress associated with deregulation of metabolism and intense proliferation. Thus, inhibitors of eIF2α both downregulate pathways required for cancer cell survival and increase expression of pro-apoptotic genes from the p53 network on transcriptional and translational levels. Conjointly, drugs-inducing ISR are candidates for combination anti-tumor therapy.

However, the role of eIF2α phosphorylation in carcinogenesis and response to chemotherapy is ambiguous [302]. It is unclear whether increased eIF2α phosphorylation associated with tumorigenesis is either a cause of carcinogenesis or a consequence of various types of stress characteristic of tumor tissue. Both inhibition and induction of ISR have been proposed as possible strategies in cancer therapy [301,302], suggesting that a moderate level of ISR in cancer cells may be required for maintaining tumor homeostasis [302].

p53's role in cellular response to stress is frequently simplified as a model where minor stress drives modest p53 activation resulting in reversible cell cycle arrest, while e.g., extensive DNA damage leads to robust p53 induction and apoptosis [303]. It is plausible that mild ISR primarily decelerates cellular proliferation and activates survival mechanisms, while stronger ISR induction is required for alternate translation of pro-apoptotic genes necessary for triggering an apoptotic response [304]. Since only select genes are translated by alternate mechanisms upon ISR induction, a regulatory role of ISR beyond a mere amplification of transcriptome changes governs the phenotypical outcome of cellular response to stress.

Pharmaceuticals triggering ISR by PP1alpha inhibition including nelfinavir (Viracept) or guanabenz (Wytensin) [305] have been used among patients for decades and are well-tolerated without notable side effects other than mild adverse events in a small proportion of cases [306,307]. Overall, the high tolerability of these drugs represents an advantage for prescribed use in combination treatments. Nevertheless, it is possible that known side effects of MDM2 inhibitors, including thrombocytopenia and neutropenia, may be further exacerbated in combination treatment with eIF2α inhibitors and must therefore be addressed in preclinical studies.

Combinations of MDM2 and proteasome inhibitors

The ubiquitin-proteasome system is responsible for degradation of over 80% of cellular proteins [308]. Increased level of metabolic activity and metabolic reprogramming in cancer cells results

in enhanced proteosynthesis and proteasomal degradation [309]. Cancer cells are more sensitive to proteasome inhibitors than normal cells [310]. Therefore, proteasome inhibition emerged as a treatment strategy for various types of hematological and solid tumors.

Crosstalk between proteasome activity and p53 pathway is manifested at many levels.

First, proteasomal degradation is the main regulatory element responsible for p53 protein accumulation and proteasome inhibition results in p53 stabilization and activation [311,312]. Second, multiple p53 target genes are involved in protein ubiquitination, including *MDM2*, *DDB2*, *FBXW7*, *TRIM32*, *MGRN1*, and *UBR5* [2,104] (Figure 2). Remarkably, very few if any of the 50 genes associated with proteasome via HUGO and KEGG databases [313,314] are deregulated on the transcript level by p53 induction, while other transcription factors modulate expression of numerous proteasome genes [315]. Third, proteasomal inhibitors induce endoplasmic reticulum stress, unfolded protein response [316], activation of double-stranded RNA-activated protein kinase (PKR)-like ER kinase (PERK), and inhibition of eIF2a [317] resulting in increased translation of select p53 target genes [52].

Proteasome inhibitors in cancer treatment are used both as monotherapies and in combination with other drugs, often in response to acquired resistance following monotherapy [318]. Various proteasome inhibitors including bortezomib (BTZ, PS-341, Velcade) [319,320], and carfilzomib (CFZ, PR-171, Kyprolis) [321,322], manifested synergistic effects with MDM2 inhibitors in multiple myeloma [320], mantle cell lymphoma [169], and liposarcoma [322] both *in vitro* and *in vivo*. Interestingly, bortezomib also rendered synergistic effects with nutlin in various p53-mutant cells [169,323,324].

Altogether, proteasome inhibition is an established strategy with cancer treatment and most successful with hematological malignancies. However, more research is needed to elucidate mechanism of individual proteasome inhibitors *in vivo*, since protein turnover is affected at concentrations much higher than achieved clinically [325]. Furthermore, our knowledge of regulatory events modulating the p53 network by selective protein degradation through various proteasome subtypes is relatively limited. Therefore, proteomic studies will be necessary to identify proteasome inhibitor for efficient use in combination with MDM2 inhibitors.

Synergies between MDM2 inhibitors and apoptotic modulators

Cancer cells elimination via apoptosis represents the most desirable outcome from combination targeted therapy [326]. Unsatisfactory levels of apoptotic response to treatment with MDM2 inhibitors, which is characteristic to most cancer types, may be caused by either insufficient induction of proapoptotic genes within the p53 network or by aberrant activity of apoptosis mediators in cancer cells increasing resistance to stimuli resulting in cell death [327,328]. Consequently, both activators of apoptotic pathways and inhibitors of anti-apoptotic proteins epitomize a logical choice for combination treatment with MDM2 inhibitors to trigger cancer cell death.

Tumor Necrosis Factor (TNF)-Related Apoptosis-Inducing Ligand (TRAIL) failed in cancer treatment when used in monotherapy, owing to expansion of resistant subpopulations. Combination treatment increases the efficiency of TRAIL within a broad range of cancer types [329,330]. Besides other compounds, TRAIL has been used successfully combined with MDM2 inhibitors in lymphoma [170], myeloma [331], lung, ovarian, and colorectal cancer models [220,332]. Similarly, p53 induction by nutlin sensitized numerous sarcoma lines to TNF-α [333] and lung adenoma to FAS ligand [334].

Targeting the intrinsic apoptotic pathway is based mainly on blocking pro-survival proteins from the Bcl-2 family (Mcl-1, Bcl-XL and/or Bcl-2) by compounds mimicking the conserved BH3 (Bcl-2 homology) domain [326,335] or indirectly by blocking degradation of pro-apoptotic members of the Bcl-2 family including BIM [336,337] or BAD [338]. A selective inhibitor of anti-apoptotic protein Bcl-2 BH3 mimetic venetoclax (ABT199) [339] exhibited synergistic effects with MDM2 inhibitor idasanutlin in both *in vitro* and *in vivo* models of acute myeloid leukemia (AML) [340] and neuroblastoma [341]. Interestingly,

idasanutlin sensitizes venetoclax-resistant neuroblastoma cells to the combined treatment [342]. However, promising efficacy of the combined treatment in the Phase 1b clinical trial (NCT02670044) revealed expansion of clones with preexisting *TP53* mutations [343].

Another BH3 mimetic Navitoclax (ABT-263) [344] synergizes with idasanutlin to induce apoptotic cell death in T-cell acute lymphoblastic leukemia (T-ALL) [345] and *ex vivo* ALL cultures [346]. Inhibitor of MDM2 brigimadlin in combination with Bcl-2 inhibitor lisaftoclax (APG-2575) [347] is currently tested in clinical trials for treatment of pediatric neuroblastoma or solid tumors (NCT05701306), salivary gland cancer (NCT03781986), AML, and myelodysplastic syndrome (NCT04275518) [348].

Endogenous Inhibitor of apoptosis XIAP downregulation by antisense oligonucleotides (ASO) synergized with nutlin to induce apoptosis in AML cells [349]. XIAP ASOs were well tolerated in clinical trials [350] contrasting with small molecule inhibitor of XIAP birinapant (TL32711) [351], causing serious adverse effects and termination of certain clinical trials. However, recently developed XIAP degraders may overcome this shortcoming of an otherwise promising group of targeted anticancer therapeutics [352]. Similarly, emerging inhibitors of antiapoptotic proteins like c-FLIP [353] open new avenues for boosting apoptotic response upon p53 induction by MDM2 inhibitors [354].

Summarily, apoptosis of cancer cells is the ultimate aim of most therapies. Pharmaceutics activating the apoptotic machinery therefore represent obvious choices when searching for synergistic drugs to use along with MDM2 inhibitors. Nevertheless, numerous challenges for both drug groups remain to be addressed, namely adverse effects, heterogeneity in tumor cell response, bioavailability, and tumor penetrance [326].

Synergies of CDK inhibitors and MDM2 inhibitors

Cell cycle arrest is a crucial cellular response to p53 induction mediated largely by the p53 target gene *CDKN1A* along with many other directly induced genes proffering anti-proliferative functions (Figure 2). Decelerated proliferation or complete disappearance of cells progressing through the S phase is the leading response to MDM2 inhibitors within cancer cell lines [163], in normal cells [355–357], in iPSCs at various stages of differentiation [358], and human embryonal stem cells [359], while other p53-mediated phenotypes like apoptosis [163] or senescence [357] manifestation seem to be more cell type- or status-dependent.

Lost control over proliferation signaling is the very essence of cancer. Throwing a wrench into the cell cycle machinery by inhibiting critical components such as cyclin-dependent kinases (CDKs) therefore represents a rational approach for cancer treatment. The human genome encodes 21 CDKs functionally divided into two main subfamilies involved in regulation of cell cycle (chiefly CDK1, −2, −4, and −6) and transcription (tCDKs including CDK7–9, −12–13, and −19) [360,361]. Inhibitors with varied specificity were developed to target kinases of both groups and tests of many compounds proceeded to clinical phases [362–365].

Wild-type p53 may contribute to antiproliferative or radiosensitizing effects of some CDK inhibitors [366–368]. Conversely, CDK4 inhibition attenuated p53-induced transactivation [368] by reducing RNA Polymerase II recruitment while p53 occupancy remained the same. Significantly, pre-treatment with CDK4/6 inhibitor palbociclib (PD0332991) [369] protected the nutlin-sensitive cell line SJSA from apoptosis [370]. Such results may cast doubts on cancer therapies based on CDK4/6 and MDM2 inhibitor combinations, yet other reports including *in vivo* studies demonstrate synergistic effects between both drug classes, suggesting context-dependent efficacies [225]. MDM2 inhibitor CGM097 [192] co-administered with CDK4/6 inhibitor ribociclib (LEE011) [371] reduced or arrested tumor growth of patient-derived xenograft (PDX) melanomas [372]. Idasanutlin and CDK4/6 inhibitor abemaciclib

evince additive effects in neuroblastoma both *in vitro* and *in vivo* [373].

In a clinical trial (NCT02343172), the CDK4/6 inhibitor ribociclib and MDM2 inhibitor HDM201 were combined to evaluate benefits to patients with locally advanced/metastatic well-differentiated/dedifferentiated liposarcoma. Upon completion of Phase Ib efforts, Novartis decided not to open Phase II owing to safety concerns [374]. Patients were treated using three different regimens with either i) low (2.5-15 mg) daily doses of HDM201 and 400 mg ribociclib on a 2 weeks on, 2 weeks off schedule with only one 4-week cycle planned, ii) high doses of HDM201 (50–-200 mg) delivered once every 3 weeks and varied doses of ribociclib (200–400 mg) in daily doses, 2 weeks on, 1 week off, in a 3-week cycle, or iii) high doses of HDM201 (100–200 mg) delivered once every 4 weeks along with varied doses of ribociclib (200–400 mg) in daily doses, 2 weeks on, 2 weeks off, in a 4-week cycle. Reported adverse events were similar to results from MDM2 inhibitors tested in previous clinical trials [181]. Despite a limited number of participants in some groups, trends suggest that lowering HDM201 to 5 mg in daily doses with 400 mg ribociclib reduced neutropenia and thrombocytopenia to ~10%, while nausea (70%) and vomiting (30%) were reported more often. With higher doses of HDM201 administered daily (15 mg) or a single high dose (150 mg), neutropenia occurred more frequently (at 71%, or at 55%, respectively), similar to thrombocytopenia reported in 29% or 27% patients, respectively. Partial response at 10% and 25% frequency has been observed in patients treated daily with 400 mg of ribociclib combined with a high single 150 mg or 200 mg dose of HDM201. Only the highest dose of 200 mg HDM201 effected increased levels of MDM2 and p21 in tumors. Owing to adverse effects, doses of both drugs were lowered or delayed for all patients in both groups. Notably, serious adverse effects were reported across the study with no obvious treatment-associated pattern. Ultimately, the HDM201 dose de-escalation approach failed to deliver desired outcome, since patient response has been limited to stabilizing the disease at best, while critical hematological adverse effects were still existing at a relatively high rate. Therefore, other strategies should be considered, including use of MDM2 inhibitors with lower hematological toxicity and prophylactic use of growth factors as with chemotherapy-induced neutropenia [375] and thrombocytopenia [376] treatment.

CDK9 inhibitor atuveciclib downregulated MDM4 and enhanced p53 activity induced by nutlin and synergized with the MDM2 inhibitor in killing A375 melanoma cells [377].

Altogether, CDK inhibitors represent a highly promising group of targeted anti-cancer drugs where novel compounds [362,363,378,379] indicate increased specificity permitting more precise focusing on cancer-relevant CDKs in combination with targeted therapy [380,381].

Targeting cancer cell metabolism in combination with MDM2 inhibitors

Metabolic alterations in cancer cells are enormous and up to some level preventable by p53 activity [382,383] which alters metabolism of numerous biomolecules implicated in cancer pathophysiology such as glucose, fatty acids, or amino acids.

Glucose is a critical source of energy for cancer cells [384,385], and p53 activity influences glucose metabolism via several mechanisms [386] including direct transactivation of *TP53*-inducible glycolysis and apoptosis regulator (*TIGAR*), a biphosphatase reducing glycolysis in cancer cells [104,387], carboxymethylenebutenolidase homolog (*CMBL*, Figure 2), a tumor suppressor gene capable of reprogramming glucose metabolism [388], Ras-Related Glycolysis Inhibitor And Calcium Channel Regulator (*RRAD*, Figure 2) [389] and miR143-mediated indirect repression of hexokinase 2 (*HK2*) [52,390]. Conversely, p53-driven repression of glucose transmembrane transporters GLUT1 (*SLC2A1*) [391], GLUT3 (*SLC2A3*) [392] and GLUT4 (*SLC2A4*) [391] on the transcript level seems to be cell type-specific and rather uncommon across various cancer lines [104] or induced pluripotent stem cells regardless of the differentiation status [234]. Illustrative of glucose essentiality for cancer cell growth is limited proliferation and viability decrease upon glucose uptake restriction [393,394]. Importantly,

combined inhibition of EGFR-driven glucose metabolism and MDM2 shows strong synergistic effects by inducing apoptosis *in vitro*, blocking tumor growth *in vivo*, and extending survival of experimental animals [395]. Effects of metformin, a glucose-lowering and insulin-sensitizing drug used widely for diabetes mellitus treatment on glucose and lipid metabolism are complex [396]. In combination with MDM2 inhibitors, metformin increased antiproliferative and pro-apoptotic effects of MDM2 inhibition in mesothelioma [397] and ovarian cancer cell lines *in vitro* [398] and decelerated tumor growth *in vivo* [398].

Perturbations of lipid metabolism in cancer cells reflect broad variety of pro-tumorigenic roles of lipids and lipid metabolites. It is unclear how p53 activity impact on lipid metabolism suppresses tumor growth [399] as a common p53 target gene ceramidase *ACER2* [400] (Figure 2) seems to play a context-dependent roles in carcinogenesis [400–403], and carboxyl ester lipase *CEL* is highly polymorphic [404] with carcinogenic mutants [405]. Other genes involved in lipid metabolism and reported as p53 targets, including Carnitine Palmitoyltransferase 1C (*CPT1C*) [406], lipin 1 (*LPN1*) [407], and Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha (*PPARGC1A*) [408] are responding to p53 induction in a cell type-specific manner [2,104]. Nevertheless, targeting lipid metabolism for cancer treatment is a relatively novel concept with no FDA-approved therapies presently available [409]. Unsurprisingly, only limited information is available regarding possible synergies between lipid metabolism-targeting compounds and MDM2 inhibitors. As reported by Miao and colleagues, nonsteroidal anti-inflammatory drugs (NSAIDs) like aspirin alter lipid metabolism and in combination with nutlin may increase cell death *in vitro* and decelerate tumor growth *in vivo* [410].

Amino acid metabolism is influenced by p53 activity via several mechanisms including cysteine hydrolase (*CMBL*) [388] gene transactivation, potent tumor suppressor [411] Peptidyl Arginine Deiminase 4 (*PADI4*) [412] (Figure 2), induction of proline dehydrogenase 1 (*PRODH*) [2,14,104,413,414], glutaminase 2 (*GLS2*) [52,104,234,415] or downregulation of glutamate/aspartate symporter *SLC1A3* [2,52,104,234]. Intriguingly, basal levels of wild-type p53 are required for maintaining SLC1A3 protein levels [416]. Since altered metabolism in cancer cells makes them dependent on some of the amino acids classified as non-essential for normal cells [417], targeting amino acid metabolism emerges as a promising avenue in cancer therapy [418]. Despite numerous compounds and amino acid analogs being developed [419], very few works currently explore possible synergy in dual targeting of cancer cell amino acid metabolic vulnerabilities along with MDM2 inhibition. Promising cell line-specific synergistic effects of nutlin and glutaminase GLS1 inhibitor CB-839 were reported by Scott and colleagues in breast tumor lines cultivated *in vitro* [414].

First reported a century ago [420], changes in metabolism represent one of the key cancer hallmarks [421] and treatment opportunity. Notwithstanding, progress in treatment targeting cancer cell metabolism has been limited because of slow novel therapeutics development [422]. Moreover, since cancer cell metabolism is using identical pathways as normal cells only much more intensely, targeting cancer cell metabolism is more likely to be successful with a combination treatment providing a sensitizing effect, rather than a single decisive impact in monotherapies.

mTOR and other growth signaling pathways in combination with MDM2 inhibitors

The mammalian Target of Rapamycin (mTOR) is a serine/threonine kinase involved in maintaining cellular homeostasis by regulating numerous cellular processes including growth factor signaling, translation, metabolism, actin cytoskeleton, and autophagy. mTOR pathway activity promotes cell growth, proliferation, survival, migration, plus immune response [423] and is frequently hyperactivated in cancer [424,425]. Unsurprisingly, numerous cross-talks between p53 and mTOR pathways have been reported [426,427]. Inhibition of mTOR pathway by p53 activity is mediated by multiple mechanisms such as PTEN/PI3K/AKT axis, Sestrin1/2 (*SESN1*, *SESN2*), TSC2, REDD1 (*DDIT4*) along with numerous microRNAs [66,426,428–434]. Conversely, mTOR pathway modulates p53 and MDM2 protein synthesis and phosphorylation [426,435].

Inhibition of mTOR by metformin exhibited synergistic effects with the MDM2 inhibitor idasanutlin on viability of mesothelioma [397] and ovarian cancer cell lines and tumor growth in experimental animals [398]. Everolimus (RAD001), an mTOR inhibitor [436], synergized with nutlin *in vivo* to suppress prostate tumor growth [437]. Inhibitor of the upstream phosphoinositide 3-kinase (PI3K) inhibitor Ly294002 sensitized acute lymphoblastic leukemia cells to nutlin-induced apoptosis [438,439], and another PI3K inhibitor idelalisib (GS-1101, CAL-101, Zydelig) [440] synergized with nutlin to induce antiproliferative effects in chronic lymphoblastic leukemia cells (CLL) *ex vivo* [441]. In glioblastoma multiforme line, MDM2 inhibitor ISA27 [442] synergized with rapamycin to decrease viability and promoted cell differentiation [443].

MEK inhibition by cytostatic drug AZD6244 (selumetinib) synergizes with nutlin to induce apoptosis in AML cell lines [444]. Interestingly, selumetinib produces promising results in a clinical trial (NCT02407405) among adult patients with neurofibromas that maintain a relatively low frequency of *TP53* mutations [445], and the MEK inhibitor pimasertib [446] evinced partial response in 4% and stable disease response in 63% of patients with locally advanced or metastatic solid tumors in combination with MDM2 inhibitor SAR405838 (NCT01985191) [199,447]. Another MEK kinase inhibitor trametinib [448] (GSK1120212, Mekinist) combined with MDM2 inhibitor KRT-232 ok [194] manifested response in 31% of relapsed/refractory AML patients in clinical trial NCT02016729 ok [200].

Protein kinase C (PKC) represents a family of serine-threonine kinases with both positive and negative effects in carcinogenesis [449]. Despite ambiguous functions of PKC isoforms in oncogenesis and their involvement with numerous physiological functions, several inhibitors were developed and tested for anti-tumor effects. In uveal melanomas, PKC inhibitor AEB071 ok [450] in combination with MDM2 inhibitor GCM097 ok [192] suppressed growth in PDX uveal melanoma *in vivo* models [451]. Other PKC inhibitors like sotrastaurin (AEB071) [450] or bryostatin 1 ok [452] elicited stronger antiproliferative effects *in vitro* when combined with MDM2 inhibitors [453,454]. Darovasetib (LXS196), a pan-PKC inhibitor with potent anti-tumor effects demonstrated in uveal melanoma xenograft model [455] has been tested in a clinical trial (NCT02601378) [456] both as a monotherapy and in combination with MDM2 inhibitor HDM201. According to the trial sponsor's statement, the combination arm was terminated because of minimal clinical activity observed at the tested doses.

Upon binding to a specific receptor, Vascular Endothelial Growth Factor (VEGF) stimulates angiogenesis in tumors, which is required for saturating metabolic needs of the growing mass. Inhibitors of VEGF signaling were therefore developed as anti-cancer therapeutics [457]. Bevacizumab (Avastin) is a monoclonal antibody blocking VEGF [458] indicated for treatment of multiple cancer types. Nutlin and bevacizumab cooperate to induce apoptosis in neuroblastoma and inhibit vascularization as well as metastasis [459].

Overall, growth signaling deregulation is the principal component of cancer development, and the PI3K/AKT/MEK axis along with mTOR are the most frequently activated cancer pathways [460]. Moreover, the same kinases are frequently implicated in treatment resistance. Therefore, targeting growth signaling pathways in combination therapy represents a highly promising strategy documented by positive outcomes of both preclinical tests and early clinical trials.

Inhibition of tyrosine kinase activity invigorates anti-tumor effects of MDM2 inhibitors

Nearly 60 members of the Receptor Tyrosine Kinases (RTKs) family regulate key cellular functions including proliferation, cellular growth, survival, migration, and differentiation [461]. Since many cancer types show "addiction" to oncogenic activity of RTKs, small molecule therapeutics were developed and approved for treatment of several cancers [462]. However, resistance to tyrosine kinase inhibitors (TKI) may be acquired [463,464], and combination therapy has been proposed as a strategy to overcome this issue [464] including combinations with MDM2 inhibitors which indicate promising results among multiple cancer types. Selective TKI imatinib (STI571)

[465] and nilotinib (AMN107) [466] which promote expression of pro-apoptotic Bim [467] sensitize CML progenitors to MDM2 inhibitors both *in vitro* and *in vivo* [468–470]. An ongoing clinical trial of combination targeted therapy in CML patients who have failed TKI (NCT04835584) utilizes a small molecule MDM2 inhibitor KRT-232 ok [194] as a sensitizer to dasatinib/nilotinib [471] treatment. Importantly, certain adverse effects of TKI including neutrocytopenia and thrombocytopenia were also reported for MDM2 inhibitors [472]. Therefore, close attention to incidence of cytopenias should be paid for any proposed combination therapy using both drug types, and TKI with reduced hemotoxicity like nilotinib may represent a more promising alternative to dasatinib, which is associated with neutropenia in 21% and thrombocytopenia in 10–19% of cases [473] and the highest hemotoxicity among 17 compared TKIs [474]. Recently, the MDM2 inhibitor idasanutlin was employed in combination with RTK inhibitor nilotinib to target residual quiescent CML stem cells which respond poorly to TKIs alone and represent a cell pool responsible for disease recurrence. Targeted activation of p53 in both blast and chronic phases of CML disabled self-renewal of this population, allowing TKI therapy discontinuation and treatment-free remission [475,476]. A phase 1/2 clinical trial (NCT04835584) is currently recruiting patients to validate this approach in a clinical setting.

Fms-related receptor tyrosine kinase 3 (FLT3) is a tyrosine receptor kinase recurrently mutated in AML (approximately in 30% of cases). Numerous FLT3 inhibitors were developed for use in AML treatment [477] including midostaurin [478] (CGP41251; PKC412; Rydapt) which inhibits not only wild-type and mutant FLT3, but also multiple isoforms of PKC, vascular endothelial growth factor 2 (VEGFR-2), and platelet-derived growth factor (PDGFR) [479,480]. In combination with the MDM2 inhibitor HDM201, midostaurin synergistically decreased viability of cells isolated from peripheral blood or bone marrow of AML patients [481]. Regrettably, a clinical trial (NCT04496999) exploring dual inhibition of FLT3 and MDM2 in AML patients has been terminated owing to insufficient recruitment and business consolidation [482]. The initial inhibitor specifically developed to inhibit FLT3 quizartinib (AC220) [483] synergized with MDM2 inhibitor milademetan (DS-3032b, RAIN-32) in exerting anti-leukemic activity, keeping all experimental animals alive for over 140 days post-implantation, whereas all controls or mice treated with individual compounds were sacrificed before day 65 after intravenous inoculation with human AML line MV-4-11 ok [484]. This finding prompted the clinical trial NCT03552029 in AML patients with FLT3 mutation. In one arm of the trial, six participants received 30 mg of quizartinib and 90 mg miladeteman daily for 7 days. Remarkably, 50% of patients showed a complete remission (with incomplete blood count recovery) and 33% disease stability. Reported adverse events included febrile neutropenia in one patient (17%), neutropenia in two patients (33%), and thrombocytopenia in one patient (17%). In general, a quizartinib and milademetan combination seems to have better results in AML patients than milademetan alone (NCT03671564). However, improved outcomes in the quizartinib/milademetan combination treatment arm over quizartinib alone (NCT02834390, NCT02039726) remain unclear and may abide in limiting hematological adverse effects of the individual compounds.

Bruton's tyrosine kinase (BTK) is a downstream mediator of the B-cell receptor pathway governing B-cell proliferation, survival, and differentiation. Small molecule inhibitors of BTK are approved by the FDA for treating B cell malignancies [485]. Nevertheless, monotherapies with BTK inhibitors such as ibrutinib (Imbruvica, PCI-32765) [486] lead to resistance [487–489]. Combination treatments were proposed to overcome resistance to ibrutinib, and MDM2 inhibitors manifested synergistic effects among preclinical studies in diffuse large B-cell lymphoma cell lines [490], in B-CLL patient samples [441,491,492], and in B leukemic mouse xenograft models [490,491].

Focal adhesion kinase (FAK) is a non-receptor tyrosine kinase involved in many cellular programs including proliferation, survival, migration, and invasion [493]. Activated by RTKs, cytokines, integrins, and numerous other stimuli, FAK serves as activation signal transducer for multiple target pathways including RAS/RAF/

ERK, JNK, SRC, YAP, and PI3K/AKT/mTOR and downstream oncogenes promoting cancer cell survival [493]. Moreover, FAK may act as molecular scaffold enhancing MDM2-dependent ubiquitination and degradation of p53 ok [494]. An inhibitor of the FAK-p53 interaction (Roslin 2, R2) increases p53 transactivational activity and blocks tumor growth *in vivo* in a p53-dependent manner [495]. Despite FAK not being an oncogene [496] or essential for cell proliferation [497], it is overexpressed in 80% of solid tumors on both mRNA and protein levels [496,498] and a major target drug in cancer treatment [493]. Inhibiting FAK using PF-562,271 [499] in combination with nutlin triggers additive antiproliferative effects in mesothelioma lines *in vitro* [500]. Another FAK inhibitor PF-573,228 synergized with nutlin to decrease survival of neuroblastoma lines *in vitro* [501].

Spleen tyrosine kinase (SYK, p72Syk) is a nonreceptor tyrosine kinase downstream of cell surface receptors such as Fc receptors, complement receptors, and integrins. SYK plays an important role in triggering immune response and allergic reactions [502]. Recently, SYK activity has been identified as essential for cancer cell survival and proliferation. Therefore, small molecule inhibitors of SYK were developed to treat various B cell malignancies [503]. Inhibitor of the SYK kinase R406 showed synergistic effects with nutlin in CLL *ex vivo* [441].

The fusion oncoprotein Bcr-Abl is an aberrant tyrosine kinase originating from reciprocal chromosomal translocation in hematopoietic stem cells causing chronic myeloid leukemia (CML) (present in 95% cases) and acute lymphocytic leukemia (ALL) (present in 35% cases) [504]. Inhibitors of Bcr-Abl like imatinib (Gleevec, Glivec, STI571) [505] represent a major milestone in targeted therapy of CML [506]. Nonetheless, resistance to imatinib may occur, and new drugs along with alternative approaches are being developed including combination targeted therapy [506]. Since p53 pathway inactivation is one of the common mechanisms of resistance to imatinib, MDM2 inhibitors were tested with Bcr-Abl inhibitors to explore anti-leukemic effects of drug combinations. Accordingly, *in vitro* assays demonstrated that nutlin synergizes with the Bcr-Abl inhibitors imatinib, nilotinib, and dasatinib to induce CML cell death [470,507]. A novel PROTAC-based drug aimed at inhibiting both Bcr-Abl and MDM2 showed similar results [508], further supporting the validity of such approach.

Overall, TKIs are mostly used for targeting deregulated hematological malignancies. Since *TP53* mutations are less frequent in hematological cancers (10–15%) [509] than in solid tumors, MDM2 inhibitors represent an auspicious choice for combination treatments.

Phosphatase inhibitors in combinations with MDM2 inhibitors

Disturbed homeostatic balance between kinase and phosphatase activity affects most oncogenic mechanisms [510] leading to occurrence and development of most cancers [511]. Therefore, along with targeting kinases, inhibiting phosphatases is emerging as a promising cancer treatment strategy. Protein phosphatase inhibitors are frequently used in combination with targeted drugs [512] including MDM2 inhibitors [513]. The p53 network accommodates several phosphatases with diverse functions. Phosphatase WIP1 is a canonical p53 target gene (Figure 2) that carries out an important regulatory role within the network [46–50]. Specific WIP1 inhibitor GSK2830371, discovered a decade ago [514], inspired numerous works exploring synergistic effects of the drug with chemotherapy [100,515–518] and various MDM2 inhibitors [52,515,516,519–525] within a broad spectrum of cancer types both *in vitro* and *in vivo*. Potent synergistic effects of WIP1 and MDM2 inhibitors reported in the pre-clinical studies have not thus far been explored in clinical trials. However, synergistic effects of the WIP1 inhibitor GSK2830371 with MDM2 inhibitors are mediated at least partly by translation inhibition [52], which can be instigated via FDA-approved drugs with high efficiency as discussed below. Notwithstanding, therapeutical use of WIP1 inhibitors has a great potential in tumors bearing activating mutations of WIP1 [100,526].

Targeting DNA damage response in combination with MDM2 inhibitors

DNA damage response (DDR) is a key mechanism in maintaining genome stability and tumor suppression. Activated by numerous upstream kinases responding to DNA damage, p53 mediates DDR by transactivating genes involved in nucleotide excision repair (NER) like Damage-specific DNA Binding Protein 2 (*DDB2*) [527] mutated in xeroderma pigmentosum group E, Ribonucleotide Reductase Regulatory TP53 Inducible Subunit M2B (*RRM2B*) [528] required for mitochondrial DNA replication and DNA repair in quiescent cells [529], or Xeroderma Pigmentosum Group C Protein (*XPC*) [530] which recognizes DNA damage in early phase of global genome NER [531] (Figure 2). Defective DDR is common in cancer cells, where it creates vulnerabilities which can be exploited in targeted treatment. The Poly (ADP-ribose) polymerase (PARP) is an enzyme critical for base excision DNA repair (BER) in rapidly dividing cancer cells [532]. Since cancer cells are often defective in other repair mechanisms like homologous recombination (HR) resulting from BRCA1/2 mutations [533,534], PARP inhibitors may be very potent anti-cancer agents in select cancer types [535]. However, acquired resistance to PARP inhibitors and high drug doses during monotherapy spurred development of combination treatments [535]. In ovarian cancer cell lines, PARP inhibitor rucaparib (AG-14447) [536] revealed synergistic effects with MDM2 inhibitors in sulforhodamine B (SRB) assay [537]. Similarly, within multiple myeloma cells, nutlin synergized with PARP inhibitor olaparib (Lynparza, AZD228, KU-59436) [538] to induce apoptosis *in vitro* [539]. Ataxia Telangiectasia Mutated (ATM) is a serine-threonine kinase activating p53 in response to DNA damage. Canonical ATM signaling promotes DNA repair, cell cycle arrest, and apoptosis. However, among advanced tumors, ATM activity may increase cell survival, proliferation, and metastasis [540]. These somewhat counterintuitive roles of ATM may explain why ATM inhibitor, KU-55933 [541] in combination with nutlin triggers apoptosis in *TP53* wild-type cell lines [542].

p53 and iron metabolism – ferroptosis induction in combination with MDM2 inhibitors

Ferroptosis is a form of non-apoptotic cell death characterized by iron-dependent accumulation of reactive oxygen species (ROS), Fenton reaction [543], glutathione (GSH) depletion, and membrane lipid peroxidation leading to cell membrane dysfunction [544,545]. It is mainly considered a tumor-suppressive mechanism, since mesenchymal and dedifferentiated cancer cells, usually resistant to apoptosis, are sensitive to ferroptosis. Nevertheless, ferroptosis may also promote cancer development by restricting the immune response in tumors [546].

Several mechanisms of p53-driven ferroptosis have been suggested, including induction of Spermidine/Spermine N1-Acetyltransferase 1 (*SAT1*) [547,548] and downregulation of ferroptosis inhibitor cysteine-glutamate exchange transporter gene *SLC7A11 ok* [549]. Expression of this transporter is regulated on multiple levels such as transcription, translation, post-translational modifications, protein stability, localization, and transporter activity [550,551]. Yet, decreases in *SLC7A11* mRNA level in response to p53 activation seems to be cell type- and stimulus-specific [2,104].

Independent of p53, MDM2 and MDMX facilitate ferroptosis by downregulating ferroptosis repressor FSP1 (*AIFM2*) and increasing lipid peroxidation [552,553]. Conversely, a suppressive role for p53 in ferroptosis may be mediated by p21/CDKN1A and cell cycle arrest protecting from GSH depletion, ROS accumulation, and cell death [554]. Moreover, joint inhibition of MDM2 and p53-induced WIP1 phosphatase brings about upregulation of heme oxygenase 1 (*HMOX1*), heme metabolization, and ferrous ion (Fe^{2+}) release [52], suggesting an alternative mechanism by which p53 may protect cells from ferroptosis.

Altogether, a common p53-driven ferroptosis program has yet to be identified, since only two upregulated (*STEAP3* and *TP53*) and two downregulated (*ACSL1* and *SLC7A11*) genes from the KEGG ferroptosis pathway (hsa04216, 42 genes) have been repeatedly modulated by p53 induction on the mRNA level [2,104]. Regardless of how

complex and context-dependent the role p53 plays in ferroptosis may be, synergistic effects between MDM2 inhibitors and ferroptosis modulators provide opportunities for combination targeted treatment resulting in cancer cell death. Erastin, a ferroptosis-inducing SLC7A11 inhibitor [555], potentiated antiproliferative effects of nutlin in Schwannoma cell lines both *in vitro* and *in vivo* [556].

Overall, modulation of ferroptosis in cancer treatment is a relatively novel concept, and more research is needed to implement ferroptosis regulators in combination therapies. Given the context-dependent role of ferroptosis in carcinogenesis, both ferroptosis inhibitors and inducers may be used in specific scenarios.

MDM2 inhibitors and immunotherapy

The main aim of cancer immunotherapy is to develop treatments improving strength and specificity of the immune system response to cancer tissue. A key strategy of this approach is suppression of negative immunomodulation mediated by the PD-1/PD-L1 pathway, which establishes and maintains immunotolerance in the tumor microenvironment [557]. Despite isolated reports of PD-1 ok [557] or PD-L1 ok [558] induction upon p53 activation, neither of the genes is a canonical p53 target [104]. In contrast, multiple studies indicate that PD-L1 is targeted by p53-induced miR-34a [559–561], resulting in suppressed proliferation and migration of cancer cells [562].

In mouse models, joint inhibition of MDM2 and PD-1 or PD-L1 blockade increased the frequency of tumor regression and led to rejection of subsequent tumor implantation [563]. Currently, several clinical trials test MDM2 inhibition combined with immunotherapy including anti-PD-1 and anti-PD-L1 antibodies [348,564,565]. Comparing the efficacy of MDM2 inhibitor brigimadlin used in monotherapy (NCT03449381) and in combination with PD-1 inhibitor ezabenlimab [566] (NCT03964233), advocacy strongly favors the latter, as the number of responding patients (partial response) doubled from 2/6 to 4/6 (durable responses), while the frequency of all types of adverse events decreased, including thrombocytopenia and neutropenia – both reduced to 1/3 of the events reported in the monotherapy group [206]. Additionally, nutlin enhanced and prolonged immunotherapy effect by maintaining large numbers of tumor antigen-presenting Ly6c +CD103+ cells [567].

Notwithstanding several drawbacks [568], immunotherapy is one of the leading treatment strategies in cancer treatment with remarkable impact on clinical outcomes [569]. MDM2 inhibitors represent an intriguing choice for combination therapies as targeted induction of p53 may both downregulate PD-L1 and increase immunogenicity of a treated tumor.

Targeting mutated TP53 in cancer treatment

In cancer tissue, *TP53* mutations occur most frequently in the DNA binding domain, typically causing single amino acid substitutions. These alterations prevent p53-mediated transactivation of downstream target genes, including the regulatory molecules MDM2 and WIP1/PPM1D. Disruption of this negative feedback loop results in accumulation of high levels of mutated p53 in malignant cells [570].

Mutant p53 has multiple effects: First, it loses its function as a tumor-suppressive network activator. Second, in early phases of carcinogenesis, it exhibits dominant-negative effects on any co-expressed wild-type variant of the transcription factor [571]. Third, gain-of-function effects have been postulated as another mechanism contributing to carcinogenesis upon *TP53* mutation.

While our review focuses on strategies for wild-type p53 activation in cancer treatment, readers interested in targeting *TP53* mutants in cancer therapy should consult several excellent recent reviews 86,87 ok [159]. Briefly, various therapeutic strategies have been proposed. Restoring wild-type p53 function can be achieved using drugs such as PRIMA-1, APR-246, ZMC-1, RITA, PEITC, or CP-313989 ok [572,573]. Cancer cells can be depleted of mutant p53 using 17AAG, Ganestespib, or Gambogic acid [573,574]. Other approaches include exploiting immunogenic properties triggered by mutated p53 ok [574] and using CRISPR/Cas9-based gene editing strategies to selectively eliminate cells with p53 mutations [574].

Importantly, approaches targeting either wild-type or mutant p53 should be viewed as complementary rather than competing strategies. While *TP53* mutations may arise during targeted therapies aimed at the wild-type molecule, restored functionality of mutated p53 can benefit from approaches that boost the tumor-suppressive power of the unmutated protein.

Conclusions

In hindsight, some of the collective expectations regarding MDM2 inhibitors were unrealistic. In response to chemotherapeutics treatment, p53 drives transcription of pro-apoptotic and promotes cancer cell death. However, direct activation of p53 by MDM2 inhibitors is insufficient in most cases to trigger apoptosis. The obvious difference is that while "dirty" chemotherapeutics cause cellular mayhem and fire up multiple stress response pathways, sole induction of p53 seems to be assessed by the cell as a likely false alarm, requiring a precautionary cell cycle arrest. Therefore, combined induction of multiple stress response pathways (e.g., ISR) may have strong synergistic effects.

Similar outcomes resulting in cell death may be achieved by combining MDM2 inhibitors with a blockade of processes that cancer cells are addicted to (aberrant growth signaling mediated by RTKs, intense protein translation and degradation, enhanced glucose uptake) or tipping the balance at the level of apoptosis regulators. Notably, p53 is involved in many cases – either in regulation of such processes through its target genes or by the p53 network possibly being directly impacted at the levels of chromatin accessibility, transcription (co-)regulation, mRNA translation, and protein degradation. Therefore, the target functional similarity principle [575] provides effective guidance in synergistic drug selection. Nevertheless, it is likely that for efficacious targeted treatment combinations, more than two drugs will be needed when strong *in vitro* effects are to be recapitulated *in vivo* [285].

Despite the intricate nature of apoptotic stress signaling, we have many reasons to believe that cancer therapies based on MDM2 inhibitors will be realized. Promising results from an expanding portfolio of drugs that synergize with MDM2 inhibitors are opening new opportunities for combinations of three (or more) targeted compounds, further enhancing treatment efficacy [285]. This approach could be particularly effective when integrated with immunotherapy and gene therapy strategies. Common adverse effects of MDM2 inhibitors reported from clinical trials complicated previous development of other targeted drug classes. Availability of proven strategies for both overcoming toxicities and increasing efficacy suggests a strong future for MDM2 inhibitors with targeted cancer therapies.

Disclosure statement

J.M.E. has provided consulting services for Elli Lily and Co. and Gilead Sciences Inc. and serves on the advisory board of Perha Pharmaceuticals. J.M.E. and Z.A. have applied as co-inventors in a provisional patent for employing dual activation of the p53 and ISR networks in cancer therapy (U.S. Provisional Patent Application 63/356,432).

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