Oncogene (2021) 40:4281–4290
https://doi.org/10.1038/s41388-021-01852-z

REVIEW ARTICLE

Shifting the paradigms for tumor suppression: lessons from the p53 field

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Received: 22 March 2021 / Revised: 5 May 2021 / Accepted: 20 May 2021 / Published online: 8 June 2021

Abstract

The *TP53* gene continues to hold distinction as the most frequently mutated gene in cancer. Since its discovery in 1979, hundreds of research groups have devoted their efforts toward understanding why this gene is so frequently selected against by tumors, with the hopes of harnessing this information toward the improved therapy of cancer. The result is that this protein has been meticulously analyzed in tumor and normal cells, resulting in over 100,000 publications, with an average of 5000 papers published on p53 every year for the past decade. The journey toward understanding p53 function has been anything but straightforward; in fact, the field is notable for the numerous times that established paradigms not only have been shifted, but in fact have been shattered or reversed. In this review, we will discuss the manuscripts, or series of manuscripts, that have most radically changed our thinking about how this tumor suppressor functions, and we will delve into the emerging challenges for the future in this important area of research. It is hoped that this review will serve as a useful historical reference for those interested in p53, and a useful lesson on the need to be flexible in the face of established paradigms.

Introduction

The importance of p53 in the control of human cancer is best exemplified by the fact that the *TP53* gene is mutated in families with the highly cancer-prone disorder Li-Fraumeni disease, and is inactivated by mutation in over 50% of sporadic human tumors [1–3]. An additional significant percentage of sporadic tumors with wild-type (WT) p53 harbor either amplification of MDM2, which negatively regulates p53 stability and function, or mutational inactivation of CDKN2A (encoding p14ARF), which positively regulates p53 signaling. It is not inconceivable that the overwhelming majority of human tumors have mutational lesions that inactivate the p53 pathway.

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p53 is involved in the regulation of numerous cancer-relevant pathways, including the regulation of genomic stability and DNA damage repair [4, 5], cell cycle arrest and senescence [6–8], apoptosis [9], metabolism [10, 11], autophagy [12], ferroptosis [13], and others. Non-transformed cells typically exhibit nearly undetectable levels of p53, but this protein is quickly stabilized in response to cytotoxic, genotoxic, or nutrient stress [14]. Once stabilized and activated via posttranslational modifications, p53 serves to protect damaged cells from malignant transformation by controlling cell fate, such as by inducing cell cycle arrest, senescence, or death [15]. A wealth of evidence supports a critical role for p53 in response of cells to stress, in particular following oncogenic stress (or that which occurs following oncogene mutation) or "environmental" stress (such as the DNA damage, hypoxia, or nutrient deprivation that may occur in non-transformed cells). It is important to note, however, that these two stresses, oncogenic and environmental, may be quite distinct in their impact on p53: for example, the p53-dependent apoptosis pathway is clearly required for tumor suppression in response to oncogene activation, such as the increased expression of the c-MYC oncogene in the Eμ-MYC mouse [16]. However, this pathway may not be required in order for basal levels of p53 to suppress

Table 1 Important genetically engineered mouse models (GEMMs) of p53.

GEMM	Consequence to cancer	References
p53 knockout ($p53^{+/-}$ and $p53^{-/-}$)	• p53 was dispensable for embryonic development • 74% of $p53^{-/-}$ mice developed cancer; only 2% of $p53^{+/-}$ mice developed tumors in the timeframe analyzed	Donehower et al., 1992
$p53^{R172H}$	• Increased mitochondrial function • Suggests a role for p53 in bioenergetic homeostasis	Liu et al., 2000 [87] Wang et al., 2013
$Csnk1a1^{floxed}$/Vil1-Cre-$ER^{T2}p53^{\Delta gut}$ $Csnk1a1^{floxed}$/Vil1-Cre-$ER^{T2}p53^{R172H}$	• Mutation R172H of p53 was oncogenic in the distal section of the gut • Mutant p53 was tumor suppressive to the proximal section of the gut	Kadosh et al., 2020
p53 "3-KR": $p53^{K117R+K161R+K162R}$	• Is unable to induce apoptosis, cell cycle arrest, or senescence • Did not form spontaneous tumors, as this protein can promote ferroptosis	Li et al., 2012 Wang et al., 2016
p53 "4-KR": $p53^{K98R+K117R+K161R+K162R}$	• Can no longer induce ferroptosis along with cell death, cell cycle arrest, and senescence • Severely impaired for suppressing tumor growth	Wang et al., 2016
p53 "S47": $p53^{P47S}$	• Maintains most p53 functions • Resistant to ferroptosis • Susceptible to spontaneous tumor formation • Increased fitness seen in S47 mice	Jennis et al., 2016 Gnanapradeepan et al., 2020
$p53^{25,26}$	• Is defective for induction of *p21*, *PUMA*, and *NOXA* • Retains the ability to suppress K-Ras^{G12D}-induced tumor growth • Is an effective suppressor of fibrosarcoma growth • Suppresses medulloblastoma and B-cell lymphoma in vivo	Brady et al., 2011 Jiang et al., 2011 [88]
p53 "Super-tumor suppressor": $p53^{53,54}$	• Retains the ability to suppress K-Ras^{G12D}-induced tumor growth • Is a super-tumor suppressor in PDAC • Negatively regulates YAP via *PTNP14* activation	Brady et al., 2011 Mello et al., 2017
$p53^{25,26,53,54}$	• This TA1/TA2 double mutant is "transcriptionally dead" • Has impaired ability to suppress K-Ras^{G12D}-induced tumor growth • Fails to suppress B-cell lymphoma development	Brady et al., 2011 Jiang et al., 2011 [88]

Shown are some of the most critical p53 mouse models that have changed the p53 field. This includes the first p53 knockout mouse, the acetylation deficient mutants $p53^{3KR}$ and $p53^{4KR}$, the transactivation mutants (TA1, TA2, and TA1/TA2 mutants), the tumor prone $p53^{P47S}$ mouse, the mutant p53 "tumor-suppressive" mouse, and the Li-Fraumeni mutant showing enhanced fitness.

spontaneous tumor formation [17, 18]. Therefore, it is important to distinguish p53-mediated tumor suppression that occurs in oncogene-driven mouse models from the suppression of spontaneous tumors in non-stressed animals (Table 1). Outlined below are some of the surprising lessons learned by the p53 field about its tumor-suppressive abilities, in loosely chronological order.

TP53 is an oncogene, and then a tumor suppressor gene

It is a well-known story in the p53 field that following the cloning of the *TP53* gene, three different groups published papers supporting the conclusion that this gene was an oncogene, and for example, could cooperate with RAS to transform cells in culture [19–22]. In subsequent years, hints that this designation was incorrect came from several groups, including the Benchimol group, who published that the murine *Trp53* gene appeared to be consistently rearranged or deleted in tumors in mice, suggestive of anticancer, not pro-cancer, function [23]. In 1989, the Levine group cloned the human *TP53* gene independently from the previous groups, and provided meticulous and compelling evidence that p53 functions as a tumor suppressor, not an oncogene [24]. Shortly thereafter, the Levine group identified that the original version of p53 that was cloned from tumor cells contained a point mutation that inactivated its tumor suppressor function [25]. Not long after that, the Harris and Vogelstein groups confirmed that *TP53* was frequently mutated in sporadic human tumors [26] and the Friend group identified germline mutations in *TP53* in Li-Fraumeni syndrome, which is a familial cancer syndrome noted by a high incidence of cancer in multiple generations, including tumors of the bone, brain, breast, blood, and adrenal cortex [27]. These findings solidified the identification of p53 as a tumor suppressor gene, not an oncogene. Indeed, the ability of mutant forms of p53 to function as an oncogene became attributed to the ability of mutant p53 to oligomerize with WT p53 and inhibit the latter in "dominant-negative" fashion.

The p53 knockout mouse is viable and fertile

In 1992, Allan Bradley and Lawrence Donehower generated the first genetic "knockout" of the *Trp53* gene in mice [28].

Given the important role for p53 in the control of cell division, the fact that these knockout mice were viable, phenotypically normal, and fertile was quite striking, as it was generally assumed that such a critical tumor suppressor might have roles in normal development. This was also quite surprising given subsequent findings that knockout mice for other tumor suppressors, like *BRCA1*, *RB*, and *WT1*, were all embryonic lethal [29–31]. Donehower and Bradley noted an extremely high rate of spontaneous tumors in these mice, with 74% of mice showing lymphomas, sarcoma, or testicular carcinoma [28]. Surprisingly, many of the common tumors that occur in Li-Fraumeni syndrome, including breast, brain, and adrenal tumors were not evident in these mice, hinting that there might be differences between harboring a mutant form of p53 and having no p53 at all.

Mutant versions of p53 show "gain-of-function"

In 1984, the Rotter group transfected a clone for mutant p53 into an Abl-driven murine leukemia line that was null for p53. Whereas the parental leukemia line injected into mice led to localized tumors that were eventually rejected, the tumors expressing mutant p53 invariably led to aggressive tumors that were lethal [32]. These data suggested that mutant p53 might exhibit oncogenic functions, or so-called "gain-of-function" (GOF), which is distinct from the ability to bind and inhibit WT p53 (dominant-negative function). Later, the Levine group conducted an experiment in which immortalized, non-transformed murine cells that were p53 null, or a human tumor cell line that was p53 null, were transfected with tumor-derived mutant forms of p53; invariably the lines containing mutant p53 were markedly more lethal [33]. The "GOF" activity of mutant p53 has been confirmed by many groups. It is important to note however that mutant p53 does not confer "GOF" activity in all tumor types [34].

p53 controls transcription-independent pathways for cell death

One of the first activities ascribed to p53, and importantly one which is lost in tumor-derived mutants of this protein, is the ability to bind to DNA in sequence-specific manner [35]. This led to many years' worth of investigations on the identification of p53 target genes with roles in downstream functions, such as *CDKN1*A for growth arrest and senescence [36], and *BAX*, *PUMA*, *NOXA*, and *BID* for programmed cell death [37–41]. At this time, however, several groups began to report evidence that p53 could induce programmed cell death in scenarios where transcriptional regulation by p53 appeared to be abrogated [42, 43]. The mechanism for this cell death was entirely unclear, until the Moll group reported that, following stress, a fraction of p53 localized to mitochondria and could directly induce the intrinsic cell death pathway by binding and inhibiting the antiapoptotic function of the Bcl-2 protein. Notably, this group found that placing a mitochondrial leader peptide onto p53 directed the majority of this protein to the mitochondria, and that this form of p53 could induce cell death and suppress tumor cell growth [44]. The group of Green went one step further, and showed that addition of purified p53 and recombinant Bax to healthy mitochondria was sufficient to induce Bax oligomerization and cytochrome *c* release, and to induce Bax oligomerization and dextran release from liposomes; notably, a transactivation (TA)-deficient mutant of p53 called QS (mutation of amino acids 22 and 23 in the human p53 TA domain) was still able to perform this function [45]. This work was followed up by the Moll group in 2003, who showed that p53 translocates to the mitochondria in irradiated thymocytes of the mouse, where it forms inhibitory complexes with Bcl-xL and Bcl-2 [46], and by Chipuk and Green, who showed that p53-dependent expression of *PUMA* induced a PUMA/Bcl-xl complex, in turn displacing p53 from Bcl-xl and promoting mitochondrial outer-membrane permeabilization [47]. Finally, the George group showed in 2004 that mitochondrial p53 could directly oligomerize the Bax-homolog BAK on purified mitochondria [48, 49]. Subsequently, Moll and colleagues showed that mitochondrial p53 also plays a role in necrosis, via interaction with cyclophilin D [50]. While there remains continued uncertainty about the contribution of the p53-mediated mitochondrial cell death pathway to tumor suppression, it is of note that tumor-derived mutants of p53 are impaired in the mitochondrial cell death pathway, suggesting that mutation of p53 in human tumors abrogates both the transcription-dependent and -independent functions of p53 in cell death (Fig. 1).

A transactivation-deficient mutant of p53 can suppress cancer in a mouse model

The p53 protein possesses at least three critical domains: (1) the DNA-binding domain, (2) the tetramerization domain, and (3) two closely linked and homologous TA domains. The Attardi laboratory generated p53 knock-in mouse models, in which the function of either the first (TA1, $p53^{25,26}$) or the second (TA2, $p53^{53,54}$) TA domains were abrogated by mutation, as well as one with both TA1 and TA2 mutated ($p53^{25,26,53,54}$). These models revealed some surprising discoveries. Specifically, the $p53^{25,26}$ mutant is largely defective for the ability to induce p53 target genes involved in growth arrest and apoptosis, including *p21*, *PUMA*, and *NOXA* [17]. Surprisingly, despite its defect in TA, the $p53^{25,26}$ mouse is still tumor suppressive against spontaneous and oncogene-induced cancers, including

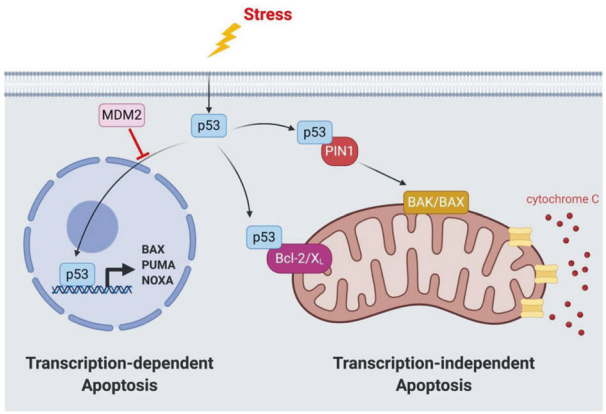

Fig. 1 Transcription-dependent and -independent mechanisms of p53-mediated apoptosis. Upon genotoxic stress, p53 is activated and can promote an apoptotic response. During transcription-dependent apoptosis, nuclear p53 transcriptionally activates proapoptotic genes, such as NOXA, PUMA, and BAX. In addition, p53 can act in a transcription-independent manner by trafficking to the mitochondria and binding to Bcl-2 and/or Bcl-xl. The prolyl isomerase PIN1 can promote p53 trafficking to the mitochondria.

K-Ras-driven lung cancer [17] and MYC-induced lymphoma [51]. Whereas the ability of the p53^{25,26} mutant to transactivate various p53 target genes is largely compromised, this mutant is still able to transactivate *BAX* [52]. Along these lines, while the p53^{25,26} mutant is unable to promote apoptosis in response to acute DNA damage, it retains substantial apoptotic activity in response to non-genotoxic stresses, such as hypoxia [52]. Collectively, these data suggested that p53 may have different mechanisms of tumor suppression depending on the cell type and cell context, including differences in the type of stress (DNA damage, serum deprivation, and hypoxia).

The Gu group generated mouse models of p53 where this protein could not be acetlayed on particular residues. The first acetylation-mutant mouse generated by Gu was p53K^{117R}, where lysine 117 in murine Trp53 (synonymous with human K120) was replaced with an arginine. This single amino acid change impaired the ability of this mutant to induce apoptosis, and the mouse did not develop spontaneous cancer, suggesting that apoptosis might be dispensable for tumor suppression by p53 [18]. In a subsequent mouse model, the acetylation sites K117, K161, and K162 were all replaced with arginine residues. In this "3-KR mouse", p53 lost the ability to transactivate the overwhelming majority of target genes, and was unable to induce cell cycle arrest, senescence, or apoptosis. Surprisingly, again these mice were not susceptible to spontaneous tumor development [18]. The combined results from several researchers therefore support the surprising conclusion that the ability of p53 to induce growth arrest/senescence and apoptosis may be dispensable, in some tissues and for some tumor types, for the suppression of spontaneous tumor development.

The ferroptosis pathway plays a role in p53-mediated tumor suppression

In order to probe the mechanism whereby the 3-KR mutant of p53 is capable of suppressing spontaneous tumor development, the Gu group performed gene expression analyses and discovered that this mutant was capable of regulating a small subset of p53 target genes with roles in ferroptosis [53]. Subsequently, they showed that cells from p53 knockout mice are resistant to ferroptosis-inducing agents, such as Erastin, while 3-KR cells remain sensitive. Moreover, it had been known that the knockout mouse for MDM2, which encodes the ubiquitin ligase for p53, was embryonically lethal, and that this was rescued by the knockout of p53 [54]. Surprisingly, the 3-KR mutant, which is largely defective in transcription except for ferroptosis genes, was also embryonic lethal in the MDM2 knockout background. Moreover, incubating embryos with ferrostatin, which inhibits ferroptosis, partially rescued this embryonic cell death [53]. The Gu laboratory then created the 4-KR mouse: K98R/K117R/K161R/K162R. They found that simultaneous loss of all four p53 acetylation sites abolished the ability of this protein to regulate the subset of genes involved in ferroptosis, including *SLC7A11* [55]. And unlike the 3-KR mouse, the 4-KR mouse is severely impaired for tumor suppression [55].

A second mouse model generated by the Murphy group further highlighted the importance of ferroptosis to p53-mediated tumor suppression. This work was on a genetic variant of p53 common in African descent populations, Pro47Ser (P47S). Cells from P47S humans, and tissues and cells from P47S mice, were capable of activating the p53 pathways of cell cycle arrest, senescence, and apoptosis (Fig. 2). Surprisingly, the P47S mouse was prone to spontaneous tumor formation, predominantly hepatocellular carcinomas and histiocytic sarcomas [56]. This group found that P47S was defective in the regulation of two genes known to be critical for ferroptosis, *GLS2* [57] and *SLC7A11*, and that P47S cells were resistant to ferroptosis induced by Erastin, due largely to increased intracellular levels of the antioxidants coenzyme A and glutathione [58–60]. These combined data further support the relevance of ferroptosis for p53-mediated tumor suppression. It is an important to note, however, that the positive role of p53 in regulating ferroptosis sensitivity is clearly cell type specific, and is best revealed under physiologically relevant nutrient levels [60]. Moreover, the ferroptotic defect in P47S cells is lost following transformation of cells with E1A and Ras [61]. Consistent with this, there is no difference in ferroptosis sensitivity in transformed MEFs that are WT and null

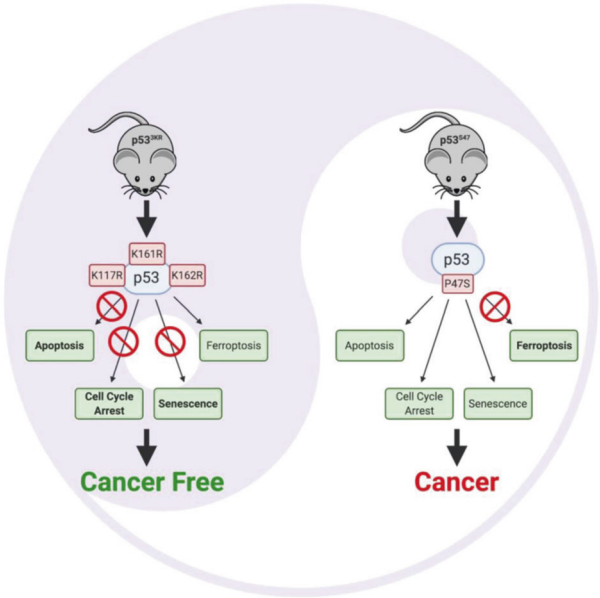

Fig. 2 Ferroptosis is implicated in tumor suppression by p53. The $p53^{3KR}$ mouse is impaired for its ability to induce apoptosis, cell cycle arrest, and senescence, yet it is still able to suppress cancer due in part to its ability to regulate ferroptosis. The $p53^{P47S}$ mouse shows enhanced spontaneous tumor formation compared to WT mice. While it can still promote apoptosis, cell cycle arrest, and senescence, cells with this variant of p53 are resistant to ferroptosis.

for p53 [62]. Indeed the relationship between p53 and ferroptosis may be reversed in tumor cells compared to non-transformed cells [63], particularly after p53 stabilization and p21/CDKN1A induction [64]. Finally, the ferroptotic pathway regulated by p53 may be independent of the key regulator of ferroptosis, GPX4 [65].

Identification of genes that are critical for p53-mediated tumor suppression

The identification of p53 target genes with roles in growth arrest and apoptosis, such as *CDKN1A*, *PUMA*, *NOXA*, *BAX*, and *BID*, initially suggested that these genes might be key contributors to tumor suppression by p53. However, these four p53 target genes are rarely mutated in human cancer, and knockout mice for these genes in mouse models failed to reveal an increase in spontaneous cancer risk [66]. Even the triple knockout of *CDKN1A*, *PUMA*, and *NOXA* fails to develop cancer [67]. Gene expression analyses have revealed the identification of hundreds of p53-regulated genes, but none that seem to contribute substantively to tumor suppression by p53.

The Attardi group examined the role of their TA-domain p53 mutant mouse models in the context of pancreatic ductal adenocarcinoma (PDAC). As expected, the $p53^{25,26,53,54}$ form of p53 behaved similar to a null allele, and these mice had a similar PDAC survival profile as $p53^{-/-}$ mice. Surprisingly, however, the $p53^{53,54}$ mouse exhibited longer pancreatic cancer-free survival compared to WT controls, indicating that this mutant protects against pancreatic cancer [68]. Transcriptomics and ChIP-Seq analysis identified roughly 100 genes that were hyper-activated by $p53^{53,54}$, compared to WT. Of those, *PTPN14* was found to play a critical role in suppressing pancreatic cellular transformation in a p53-dependent manner, by negatively regulating the YAP oncoprotein. More recently, this group used a similar approach using TA-deficient mouse models combined with a CRISPR screen to identify *ZMAT3* as a p53 target gene whose silencing largely phenocopies p53 loss with regard to transformation [69]. ZMAT3 controls splicing, including the splicing of CD44, a cell adhesion gene and stem cell marker that controls tumorigenesis [70]. These findings highlight the usefulness of genetically engineered mouse models of p53 for the delineation of key activities and target genes for p53-mediated tumor suppression (Table 1).

Mutant p53 is tumor suppressive under certain circumstances

Mutant forms of p53 can actively contribute to transformation by at least three different mechanisms: (1) loss-of-function mutations impair the ability of p53 to activate classical p53 target genes involved in growth arrest and cell death (2) mutant forms of p53 exhibit dominant-negative effects toward the WT p53 allele, and (3) mutant forms of p53 exhibit GOF properties in metastasis, transcription, and cell signaling that positively contribute to the transformed properties of the tumor cell [71]. Recently, however, even this paradigm was shattered when the Ben-Neriah group showed that tumor-derived mutant forms of p53 could retain tumor suppression function in certain scenarios. This group set out to determine the role of two "hotspot" GOF mutations, mouse R172H and R270H (equivalent to human R175H and R273H) in two mouse models of WNT-driven intestinal cancer. As predicted, (1) p53 null mice recapitulated the expected dysplasia throughout the GI tract, and (2) mutant p53 exhibited oncogenic GOF function in the distal part of the gut (ileum and colon). However, this group made the rather remarkable discovery that these tumor-derived mutant forms of p53 displayed profound tumor-suppressive function in the proximal part of the gut (duodenum and jejunum). Specifically, $p53^{R172H}$ enhanced tumor development in the colon, yet simultaneously reduced the tumor burden in the proximal gut [72] (Fig. 3). One possibility for this finding was that mutant p53 might retain transcriptional function in the duodenum and jejunum. However, ChIP-Seq analysis revealed almost complete abrogation of sequence-specific binding of mutant p53 to chromatin [72]. Rather, the authors found that mutant p53 could suppresses WNT signaling in the jejunum, due to its ability to disrupt the

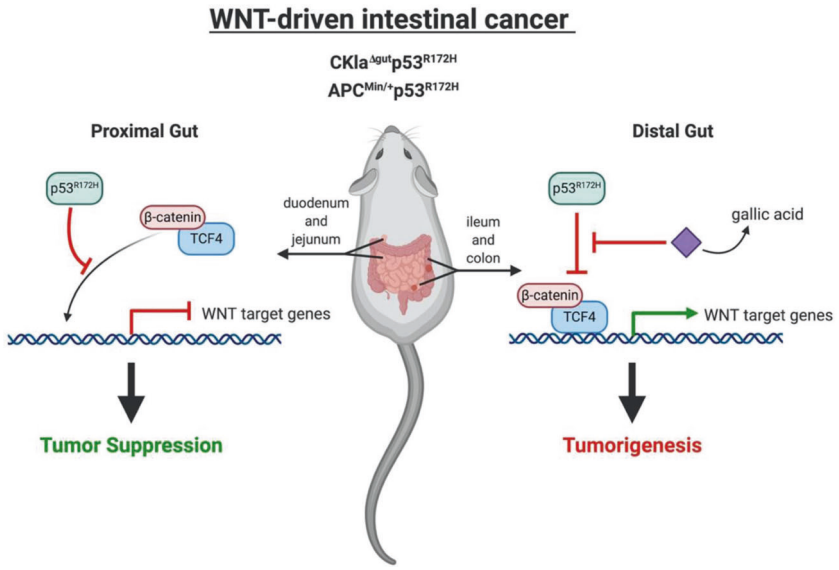

Fig. 3 Mutant p53 shows paradoxical transformation and tumor suppression in GEMM models of intestinal neoplasia. WNT-driven intestinal cancers caused by either Csnk1a1 deletion or Apc^{Min} mutation combined with the mouse p53-R172H mutation have contrasting tumorigenic outcomes in different regions of the gut. In the proximal gut (duodenum and jejunum), the presence of mutant p53 abolishes TCF4 binding to chromatin at WNT target promoters, leading to a decrease in oncogenic WNT transcription. Whereas mutant p53 is tumor suppressive in the proximal gut, mutant p53 has an opposing oncogenic effect in the distal gut (ileum and colon). Bacteria-derived gallic acid in the distal gut is sufficient to reestablish TCF4 binding to chromatin, increase expression of WNT oncogenic drivers, and promote tumorigenesis.

ability of the TCF4 transcription factor to bind to chromatin, and to regulate the WNT pathway. The differences in mutant p53 function in the proximal and distal parts of the gut turned out to be controlled by the gut microbiome, which shows increased population in the distal colon. The authors found that gallic acid produced by the microbiota in the distal colon prevented the ability of mutant p53 to function as a tumor suppressor in this region of the colon. Notably, the authors then "sterilized" the guts of mice containing mutant p53, and tumor suppression in the distal colon was lost, until they supplemented these mice with gallic acid. The take-home message is that mutant p53 is capable of suppressing tumor growth under certain circumstances. This suggests that there may be certain cancer types that never select for mutant p53 because of retention of tumor suppressor activity: an interesting place to test this hypothesis would be in the tumor types that rarely mutate p53, such as hematopoietic malignancies, renal cell cancer, or neuroblastoma. It may also explain why mutation of p53 occurs as a late event in some cancers, but an early event in others.

People and mice harboring germline mutations in p53 are more physically "fit"

Li-Fraumeni syndrome is a devastating disorder caused by germline *TP53* mutations, and resulting in a variety of early-onset sarcomas and carcinomas. Early clinical observations that individuals with Li-Fraumeni syndrome who survived cancer tended to be leaner and more fit prompted the Hwang laboratory to analyze metabolism and physical fitness in humans and mice with mutations in p53. This group discovered that cells from humans and mice with mutant p53 displayed increased mitochondrial content, along with increased capacity for physical fitness and muscle recovery [73]. These findings were the first to show that while p53 mutations confer increased cancer risk, it may lead to other, potentially positive, attributes. Similar observations were made by the Murphy group, who showed that mice containing the cancer-predisposing P47S variant displayed increase mass and increased fitness, due to the increased activity of the master regulator of metabolism mTOR [60]. The Murphy group also found that the ferroptosis-defective P47S variant is associated with increased iron accumulation in cells, and is associated with markers of Iron Overload in African Americans; conversely, this genetic variant is associated with decreased severity of malaria symptoms [59]. Taken together, these findings support the premise that alterations in the p53 pathway that increase cancer risk may show positive selection with regard to fitness and malaria resistance. These results fit with an emerging paradigm that certain cancer-associated genetic variants can provide positive selection benefit [74]; for example, BRCA1/2 carriers, who have significantly increased lifetime risk of breast or ovarian cancer, also exhibit enhanced fertility [75].

Mutant p53: drugging the undruggable

Because the p53 tumor suppressor is mutated in approximately half of all human cancers, it is an attractive target for cancer therapy. Approximately one third of p53 mutations are considered destabilizing to the protein, leading to increased denaturation and misfolding. In 2002, the Fersht group showed that a small peptide could restore the highly destabilizing I195T mutant to near WT p53 activity [76]. This laboratory also showed that the Y220C mutation, the ninth most frequent p53 cancer mutant, creates a surface crevice, thus leading to a highly destabilized protein [77]. Using in silico screening based on the crystal structure and NMR, the Boeckler group discovered a lead compound, PhiKan083, that binds to the cavity of the Y220C mutant, in turn raising the melting temperature and decreasing the rate of thermal denaturation, thus stabilizing the WT conformation of this mutant [78]. More recently, the Levine and Carpizo groups discovered that the compound NSC319726 is capable of causing zinc binding and refolding of the common R175H mutant back into WT conformation, thus restoring sequence-specific p53 transcription. This compound suppressed tumor formation in xenografts and in transgenic mouse models, and was shown to function via (1) reestablished zinc binding to p53, which is critical for p53 to bind to DNA, and (2) ROS-induced p53 posttranslational modifications.

While the restoration of WT function to mutant p53 with small molecules is an attractive therapeutic strategy for cancer [79], there remains the distinct possibility that not all p53 mutations may benefit from such p53 reactivating compounds. There has been evidence suggesting that cancer cells may be "addicted" to mutant p53 [80]; thus, it is logical that ablation of mutant p53 may be a rational therapeutic strategy for these tumor types. Two groups have recently shown that this may indeed be the case in the context of colorectal cancer (CRC), where over half of all CRCs are known to have p53 mutations. The Moll group showed that the R248Q mutant, the most common mutant in CRC, exerts GOF properties and tumor addiction. Furthermore, they showed that treating tumor-bearing mice with the HSP90 inhibitor 17-AAG suppressed mutant p53 levels and tumor growth [81]. More recently, the Murphy group showed that a novel HSP70 inhibitor decreased the expression of mutant p53 in CRC cells and in xenograft models [82]. Collectively, these findings support the premise that targeting the dependency of mutant p53 in CRC is an attractive therapeutic strategy [83], which may be applied to other cancer types, such as breast cancer [84].

Concluding remarks and future directions

Human cancer has been broadly depicted as having several critical trademarks, coined "the hallmarks of cancer": resisting cell death, inducing angiogenesis, enabling replicative immortality, activating invasion and metastasis, evading growth suppressors, and sustaining proliferative signaling, among others [85]. Loss of WT p53, and/or mutations in p53, affect the majority of these cancer hallmarks. Over 40 years have passed since the seminal discovery of the *TP53* gene, yet new and profound discoveries still affect the way p53 is understood. With over half of all human cancers harboring a p53 mutation, it remains clear that a complete understanding of p53 function will be critical to properly targeting it in the context of cancer treatment. The "classical" functions of p53 have been revealed in depth, yet to this day, it remains uncertain as to which biological pathway(s) regulated by p53 are absolutely critical for tumor suppression. The regulation of p53-mediated tumor suppression occurs on many levels: transcriptional activation of p53 targets genes critical for tumor suppression [86], transcription-independent activation of the mitochondrial cell death program [87], posttranslational modifications that can dictate the apoptosis versus senescence outcomes [88], the regulation of protein stability via MDM2, and p53 activity via protein–protein interactions [89]. Another added layer to this complexity is the tissue and cell-type-specific roles of p53, along with emerging roles for p53 in immune function. For example, the Vousden group has shown that the loss or mutation of p53 can affect the recruitment and the activity of immune cells, in turn allowing immune evasion and cancer progression [90, 91]. In light of recent advances in the field of immuno-oncology, it will be interesting to determine which mutant p53 tumors may, or may not, benefit from immune checkpoint inhibitor therapy. In support of this, several groups have shown that expression of mutant p53 in human lung cancer correlates with PD-L1 expression [92–94]. Thus, there is a clear but not fully defined role of mutant p53 in immuno-oncology that must be unraveled to identify novel therapeutic strategies for cancers with mutant p53.

Recent evidence points to the notion that certain p53 mutations can promote neo-antigens on the surface of tumor cells that could lead to novel immune-therapeutic approaches. Elaborate work recently published by Hsiue and colleagues showed that the R175H mutant of p53 allows the formation of a peptide–HLA complex on the surface of tumor cells [95]. However, this peptide–HLA complex is expressed at extremely low levels on the surface of tumor cells. To circumvent this issue, this group generated a bi-specific antibody that fuses the antibody fragment recognizing mutant p53 with a fragment that binds to the CD3 receptor complex on T cells. Notably, this reagent led to tumor regression in mouse models of multiple myeloma [95]. These data raise the possibility that therapy may be tailored for other p53 mutations. In sum, harnessing the power of the immune system, along with the ongoing

research to target individual p53 mutations, may be the key in providing improved, and longer-lasting, outcomes for cancer patients.

Acknowledgements This work was supported by the National Institutes of Health (R01 CA201430 and CA102184 to MEM, and K99 CA241367 to TB). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors would like to apologize for all the investigators whose references could not be included in this article due to space constraints. The authors would also like to thank Keerthana Gnanapradeepan, Jessica C. Leung, and Joshua L. D. Parris in the Murphy lab for assistance and thoughtful discussions. Figures were created with BioRender.com under a paid subscription to AI.

Author contributions Conception and design of the review: MEM. Generation of the figures: TB and AI. Drafting of manuscript: all. Proofing and revision of manuscript: all.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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