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REVIEW

Complexes formed by mutant p53 and their roles in breast cancer

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Abstract: Breast cancer is the most frequently diagnosed malignancy in women, and mutations in the tumor suppressor p53 are commonly detected in the most aggressive subtypes. The majority of *TP53* gene alterations are missense substitutions, leading to expression of mutant forms of the p53 protein that are frequently detected at high levels in cancer cells. P53 mutants not only lose the physiological tumor-suppressive activity of the wild-type p53 protein but also acquire novel powerful oncogenic functions, referred to as gain of function, that may actively confer a selective advantage during tumor progression. Some of the best-characterized oncogenic activities of mutant p53 are mediated by its ability to form aberrant protein complexes with other transcription factors or proteins not directly related to gene transcription. The set of cellular proteins available to interact with mutant p53 is dependent on cell type and extensively affected by environmental signals, so the prognostic impact of p53 mutation is complex. Specific functional interactions of mutant p53 can profoundly impact homeostasis of breast cancer cells, reprogramming gene expression in response to specific extracellular inputs or cell-intrinsic conditions. The list of protein complexes involving mutant p53 in breast cancer is continuously growing, as is the number of oncogenic phenotypes in which they could be involved. In consideration of the functional impact of such complexes, key interactions of mutant p53 may be exploited as potential targets for development of therapies aimed at defusing the oncogenic potential of p53 mutation.

Keywords: protein–protein interactions, mutant p53 gain of function, targeted therapy, cancer-cell homeostasis

Introduction

The *TP53* gene is the most frequent target for mutation in human cancer, and *TP53* mutations are associated with malignancy and adverse prognosis.[1,2] According to the Catalogue of Somatic Mutation in Cancer (COSMIC), approximately 23% of human breast cancers display *TP53* mutation, and this value oscillates from >80% in basal-like to <15% in luminal A subtypes.[3,4] The critical implication of *TP53* gene mutation in development of breast cancer is reinforced by the frequent occurrence of this cancer in Li–Fraumeni syndrome, a hereditary tumor-predisposing disorder associated with germ-line *TP53* mutations.[5]

The predominance of mutations with respect to deletions indicates that *TP53* mutations may confer a selective advantage during cancer development. Tumor-associated *TP53* alterations are most frequently missense mutations, leading to substitution of a single amino acid in the p53 protein.[2,6] The majority of missense mutations occur

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within the DNA-binding domain of p53, impairing its sequence-specific interaction with target gene promoters.[2] This implies loss of p53-transcriptional activity and related oncosuppressive responses. Because p53 normally acts as a tetramer, mutant p53 (mutp53) proteins may also act as dominant inhibitors of a remaining wild-type p53 allele. However, most importantly, mutations in the structured core of p53 can have significant consequences on its capability to establish novel protein interactions, and this may be a crucial step in the acquisition of oncogenic properties by mutp53, a phenomenon defined as "gain of function", or GOF.[6]

Mutp53 protein complexes as mediators of breast cancer aggressiveness

In breast cancer, mechanisms supporting primary tumor growth and survival, as well as features required for metastasis to secondary sites, can all be linked to mutp53 GOF.[6,7] Many such oncogenic functions have been ascribed to interactions between mutp53 and other transcription factors, determining specific gene-expression programs. In addition, some mutp53 oncogenic activities rely on its association with partners not involved in gene transcription. In any case, formation of protein–protein interactions appear to be a crucial element of mutp53 GOF.

One compelling open question, therefore, regards whether different mutp53 mutants might have distinctive functions, depending on the specific conformational change imposed by each mutation. In fact, different p53 missense mutants may have different affinity for interacting proteins, generating phenotypic differences in their GOF.[8] Indeed, knock-in mice expressing different p53 mutants display distinct cancer phenotypes, confirming that missense p53 mutations may have diverse biological effects.[9,10] It should also be considered that a sizeable number of tumor-associated *TP53* mutations fall outside the DNA-binding domain, potentially affecting protein conformation, tetramerization, and/or posttranslational modifications, impinging on mutp53 interactions in additional ways. Nonetheless, evidence has demonstrated that different p53 mutants can interact with the same transcription factors or proteins, activating identical target genes, and modulating the same signaling pathways.[8,11] Therefore, it remains an open challenge to define the specific impact of p53 mutations found in real tumors and to distinguish such activity from a more general pro-oncogenic action that depends on features common to all "misfolded" mutp53 proteins.

The accumulation of mutp53 observed in malignancies is also critical for its functions, suggesting that not only the altered conformation but also the increased amounts of mutp53 favor formation of nonphysiological complexes that contribute to the oncogenic phenotype.[12] In line with this concept, various groups have provided evidence of prion-like behavior of cancer-associated p53 mutants: mutp53 accumulates in heterogeneous protein complexes composed of amorphous aggregates, oligomers, and amyloid-like fibrils that are involved in breast cancer progression.[13,14] Several proteins found in mutp53 aggregates are involved in oncogenic processes, including cell metabolism, inflammatory response, RNA processing, and regulation of proteotoxic and oxidative stresses.[15]

Whatever the mechanism and potential elements of specificity, it is legitimate to generalize that interaction with mutp53 can either potentiate the oncogenic activity of tumor promoting factors or destabilize the tumor suppressive action of oncosuppressors.[6,8] There is a significant amount of literature on protein interactions of mutp53 in cancer, many of which can mechanistically explain some aspects of the GOF. Here, we focus exclusively on mutp53 interactions that have been detected in breast cancer models (Table 1). More general features of mutp53 GOF have been recently reviewed elsewhere.[8,16–18]

By forming complexes with other transcription factors, mutp53 reprograms gene expression in cancer cells

It is well established that mutp53 can profoundly alter the gene-expression profile of the cancer cell.[6,18] Various evidence has suggested that mutp53 binds DNA, thus raising the possibility that some mutp53 proteins can recognize a unique response element.[19] Nevertheless, a consensus sequence for mutp53 binding has not been identified.[6,20] Rather, mutp53 has been found to interact with other transcription factors, enhancing or subverting their normal activity, thereby changing the expression profile of their target genes.

For example, in human breast cancer cells, mutp53 binding with the transcription factor E2F1 leads to transcriptional activation of ID4, which in turn promotes neovascularization of breast tumor tissue.[21] Similarly, mutp53 binding with E2F4 causes downregulation of genes involved in DNA repair,[22] promoting cell survival and escaping apoptosis. Perhaps the best-characterized transcriptional partner of mutp53 is NFY. Studies in human breast cancer cell lines have shown that mutp53 interaction with NFY neutralizes the cell-cycle checkpoint following low levels of DNA damage.[23] Under these conditions, DNA TopBP1 recruits mutp53 and the cofactor p300 to mediate their binding with NFY, and stimulates

Table 1 List of published mutant p53 interactions and their functional impact

Interactor	Biological effect	Reference(s)
Transcription factors: positive regulation/cooperation		
E2F1	ID4-dependent induction of proangiogenic mediators; enhanced angiogenesis	21
E2F4	Downregulation of DNA-repair genes; less efficient DNA-damage repair	22
ETS1	Upregulation of drug-resistance genes	88
ETS2	Upregulation of nucleotide biosynthesis genes; improved chemoresistance	89, 90
HSF1	Heat-shock gene transcription; enhanced resistance to proteotoxic stress	33
MAFF	Repression of secreted IL1Ra; increased IL1 signaling and tumor growth	91
NFY/p300/TopBP1	Upregulation of cell-cycle genes; enhanced chemoresistance and cell survival	23, 24
NFY/YAP	Enhanced YAP activity; transcription of proproliferative and prosurvival genes	26
NRF2	Transcription of genes encoding proteasome machinery	30
PELP1	Recruitment of mutp53 on its target genes; chemoresistance	25
SP1	Transcription of ENTPD5; enhanced folding and secretion of *N*-glycoproteins	35
SREBP2	Transcription of mevalonate pathway and fatty-acid biosynthesis genes; enhanced cell motility and self-renewal; mutp53 stabilization	27, 29, 87
VDR	Altered transcriptional response to vitamin D_3; resistance to apoptosis	34
Transcription factors: negative regulation/inhibition		
p63	Inhibition of TAp63 transcriptional activity; enhanced invasive phenotype	40, 42, 43
p63–SMAD complex	Inhibition of TAp63-target genes (Sharp1/cyclin G2); enhanced invasive phenotype	43
p73	Reprogrammed p73-transcriptional activity; inhibition of apoptosis	37, 48, 49
Mediators of genomic stability and chromatin-remodeling complexes		
Mre11	Disruption of Mre11–Rad50–NBS1 (MRN) complex, impaired ATM activation; defective DNA double-strand break (DSB)-response pathways	55
SWI–SNF complex	Enhanced VEGFR2 expression; enhanced VEGFR2 signaling, cell proliferation, and migration	59
Cytoplasmic interactors		
AMPK	Enhanced aerobic glycolysis in response to energy stress; increased tumor growth and invasion	64
DAB2IP	Enhanced cell invasion and survival in response to inflammatory stimuli; augmented proliferation and invasion upon insulin stimulation	62, 63
Rac1	Enhanced Rac1 activity by preventing Rac1 de-SUMOylation; enhanced growth and metastasis of tumor xenografts	65
Positive regulators of mutant p53 stability and activity		
BAG2/BAG5	Inhibition of mutp53 ubiquitination and degradation by MDM2	75, 76
Pin1	Enhanced mutp53-dependent inhibition of p63; cancer growth and invasion	45
Plk2	Enhanced mutp53–NFY–p300 complex formation; increased expression of cell-cycle genes	77
Pontin	Augmented mutp53-transcriptional activity; enhanced cell migration and invasion	79
HSP90	Increased mutp53 stability and accumulation	70
HSP70	Inhibition of mutp53 ubiquitination and degradation by MDM2	74
Negative regulators of mutant p53 stability and activity		
ATF3	Prevents mutp53 interaction with p63; reactivates p63 function, with decreased drug resistance	92
CHIP	Stimulates mutp53 degradation	68
Mdm2	Stimulates mutp53 degradation	69

transcription of genes involved in chemoresistance, cell-cycle progression, and cell proliferation.[24] More recently, Krishnan et al demonstrated that the oncogenic coregulator PELP1 is necessary for the efficient recruitment of mutp53 on NFY target genes upon DNA damage.[25] In triple-negative breast cancer (TNBC) cell models, knockdown of PELP1 improves the chemotherapeutic response, inhibiting cell-cycle progression and activating apoptosis (Figure 1A).

A molecular circuit involving mutp53–NFY links lipid metabolism to the control of cell proliferation and tumor-tissue architecture (Figure 1B). This involves interaction with another transcription factor, YAP, a master regulator of tissue growth; formation of a YAP–NFY–mutp53 complex in human cancer cells drives transcription of prosurvival and proliferative genes, also promoting acquisition of invasive features.[26] The function of this complex in breast cancer is finely regulated by lipid metabolism and mechanotransduction. First, both in physiology and malignancy, the activation of YAP is robustly controlled by the mevalonate pathway.[27] Inhibition of the mevalonate pathway by pharmacological treatment with statins, a class of drugs used to lower cellular cholesterol levels, counteracts YAP/TAZ nuclear activity,

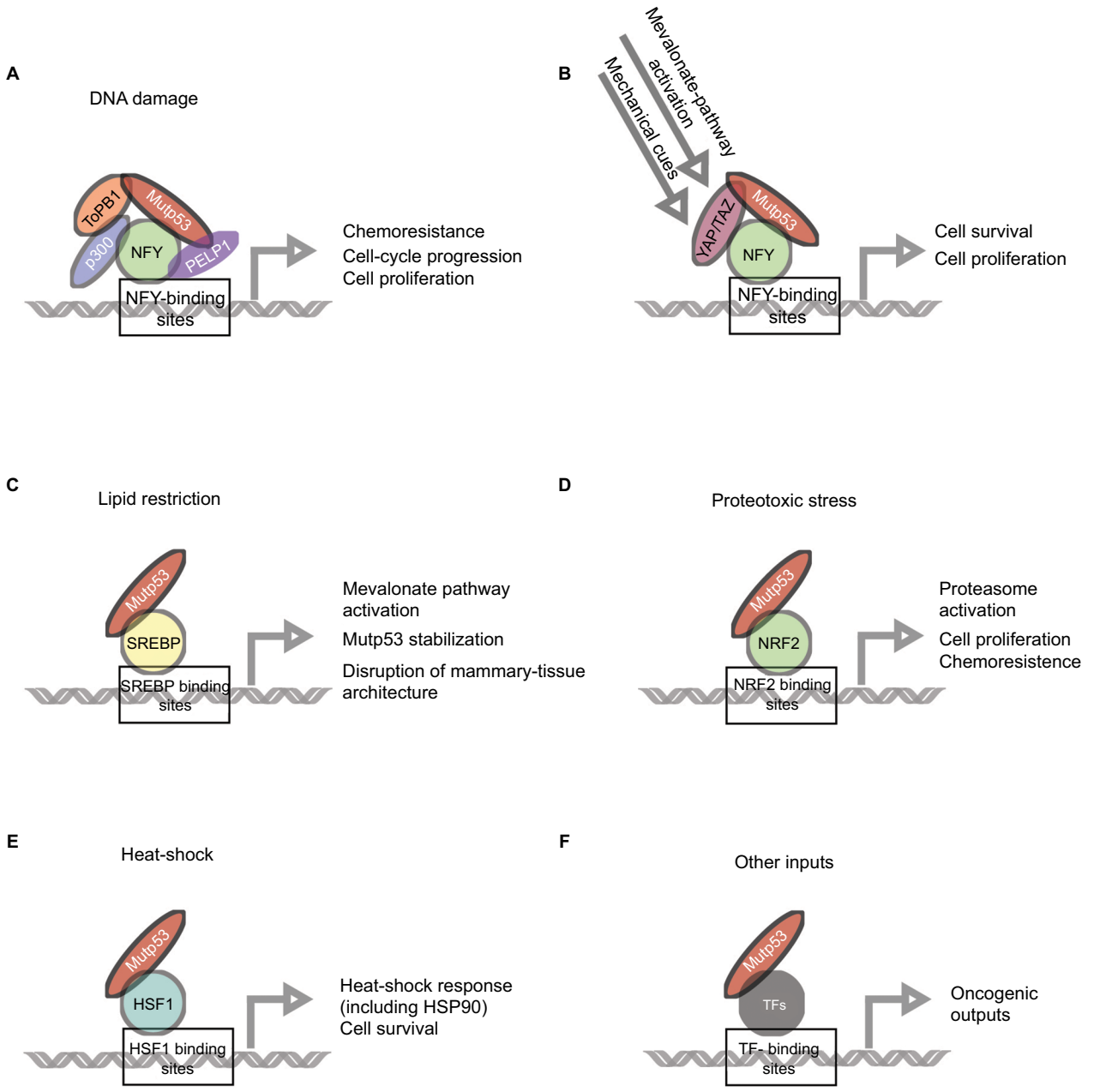

Figure 1 Mutant p53 (mutp53) interacts with various transcription factors (TFs) to reprogram gene expression in cancer cells.
Notes: (**A**) Mutp53 forms a complex with NFY, p300, PELP1, and TopBP1 to control expression of genes involved in cell proliferation and in resistance to DNA-damaging drugs.[23–25] (**B**) Mutp53 binds with YAP and NFY on the promoters of genes involved in cell growth and proliferation; both mechanical inputs and activation of the mevalonate pathway control formation and activity of this protein complex.[26–28,87] (**C**) By interacting with SREBP2, mutp53 controls expression of enzymes involved in the mevalonate pathway, promoting cholesterol and fatty-acid biosynthesis, sustaining disruption of mammary-tissue architecture, and inhibiting mechanisms of mutp53 degradation.[27–29,87,93] (**D**) By interacting with NRF2, mutp53 controls expression of multiple subunits of the proteasome, alleviating proteotoxic stress and accelerating turnover of cell-cycle inhibitors.[30] (**E**) In a complex with HSF1, mutp53 controls expression of chaperones and heat-shock proteins that in turn promote mutp53 stability.[33] (**F**) Mutp53 may interact with additional transcription factors, potentially controlling expression of different gene sets, to mediate its oncogenic gain of function.

blunting the pro-oncogenic potential of mutp53.[26,27] At the same time, mutp53 accumulation in breast cancer cells is sustained by RhoA geranylgeranylation downstream of the mevalonate pathway and by an actin-dependent transduction of mechanical inputs, sensing the stiffness of the surrounding tissue.[28] In breast cancer cells, pharmacological inhibition of geranylgeranyl transferase 1 phenocopies the effects of statins, counteracting mutp53 GOF.[28]

Another important functional link between mutp53 and cellular lipid homeostasis relies on its capability to boost the mevalonate pathway and fatty-acid intermediates, by binding the SREBP family of transcription factors, master regulators

of fatty-acid and cholesterol biosynthesis.[29] Forming a complex with SREBP2, mutp53 enhances expression of SREBP target genes, reprogramming cancer-cell metabolism via induction of the mevalonate pathway, leading to the disruption of normal mammary-tissue architecture.[29] In addition, the mutp53–SREBP complex indirectly potentiates nuclear localization and activation of YAP/TAZ in a positive-feedback loop (Figure 1C).[27] Therefore, by forming complexes with YAP, NFY, and SREBP, mutp53 can coordinate lipid metabolism, responses to mechanical cues (such as stiffness of the extracellular matrix), and a global pro-oncogenic transcriptional program, favoring tumor growth and metastasis.

Mutp53 can also affect cellular homeostasis by upregulating proteasome machinery, with a negative impact on tumor-suppressive mechanisms. This action relies at least in part on its interaction with the transcription factor Nrf2, characterized in human TNBC cells (Figure 1D). Upon protein stress, such as that induced by proteasome inhibition or by oxidants, mutp53 binds Nrf2 to enhance transcription of proteasome genes. This alleviates the protein load and favors proteasomal degradation of tumor-suppressor proteins involved in proliferation control and apoptosis, thus resulting in a pro-oncogenic response.[30] Importantly, Nrf2 acts as a master regulator of oxidative stress response. Lisek et al very recently reported that mutp53–Nrf2 interaction not only promotes expression of proteasome subunits but also coordinates transcription of a specific subset of Nrf2-dependent antioxidant-response genes, supporting survival of breast cancer cells.[31]

Interestingly, mutp53 can endow cancer cells with augmented tolerance to proteotoxic stress by activating transcription factors that are physiologically inhibited by the wild-type p53 protein. For instance, wild-type p53 negatively regulates the cytoprotective functions of the heat-shock protein HSF1, facilitating the induction of cell senescence upon DNA damage.[32] In human TNBC cells, via direct interaction with HSF1, mutp53 promotes transcription of HSPs and broadly enhances oncogenic signals via HSF1 activation, thus providing survival advantages (Figure 1E).[33]

Along this line, mutp53 interaction with the zinc-finger VDR provides another example of how transcriptional complexes involving mutp53 can dramatically subvert cell response to various inputs. In fact, mutp53 has been reported to bind VDR and p300, and this complex converts the cytotoxic effect of vitamin D3 into an antiapoptotic stimulus in human breast cancer cells.[34]

Finally, in human pancreatic and breast cancer cell lines, it has been recently shown that mutp53 can be recruited by SP1 on the promoter of the gene *ENTPD5* to induce its expression. ENTPD5 is an enzyme involved in *N*-glycoprotein folding via the calnexin–calreticulin cycle in the ER; mutp53-induced expression of ENTPD5 may favor or accelerate folding and cell-surface localization of prometastatic receptors and ligands, eventually supporting tissue remodeling, extracellular matrix invasion, and lung colonization in breast cancer.[35]

The emerging picture is that mutp53 can control gene expression by binding other transcription factors, changing their activity or influencing the selection of target genes. It is likely that additional such partners of mutp53 will be discovered in the near future, further increasing the complexity of its transcriptional impact (Figure 1F).

Binding other p53 family members, mutp53 subverts their tumor-suppressive transcriptional activities

The interaction of mutp53 with transcription factors can also be inhibitory. The best-understood example of this phenomenon is mutp53 inhibition of other members of the p53 family – p63 and p73.[36] Multiple studies collectively suggest that conformational changes in the p53 core domain cause its interaction with p63/p73.[37–39] Mutp53 binds DNA through p63 interaction, though at sites distinct from those that p63 would normally bind.[40] Mutp53–p63 association impairs TAp63-transcriptional activity, hindering its metastasis-suppressor functions.[41–43] The capacity of mutp53 to bind and counteract p63 tumor-suppressive function is itself controlled at different levels, with the involvement of additional partners and intrinsic and extrinsic signals. For example, TGFβ acts in concert with oncogenic Ras to induce the assembly of a ternary complex in which Smad2 serves as an essential platform, facilitating the interaction between mutp53 and TAp63, in both human and murine cell models. This protein complex leads to the inhibition of p63-dependent expression of two important suppressors of metastasis, Sharp1 and cyclin G2, fostering invasion of tumor cells.[43] Similarly, phosphorylation-dependent isomerization by Pin1 favors mutp53 interaction with TAp63 in TNBC cells, contributing to define a proinvasive transcriptional program that can stratify breast cancer patients according to recurrence-free survival.[44,45] Mutp53-mediated suppression of p63-transcriptional activity also results in enhanced RCP-driven recycling of the $\alpha_5\beta_1$ integrin and EGFR. This activates Rho and PKB/Akt to promote cell migration and invasion.[42] Enhancement of PI3k–Akt signaling mediated by integrin/receptor recycling also promotes the activation of

WIP, which stimulates the oncogenic phenotype by enhancing YAP/TAZ stability.[46,47]

P53 mutants also interact with multiple p73 isoforms,[48] reprogramming their transcriptional activity and counteracting apoptosis.[37,49] Various p53 missense mutants (R175H, Y220C, and R248W) have been demonstrated to bind with p63, and also p73 in human cancer cells, to subvert the transactivation of target genes.[37,38] In transgenic mice, stable expression of mutp53 (R172H) in the mammary gland reduces both basal and DNA-damage-induced apoptosis;[50] pharmacological inhibition of mutp53 restores apoptosis induction via p73 reactivation.[51–53] Finally, a study carried out in pancreatic cancer models, but also confirmed in breast cancer cells, uncovered a role for mutp53 in enhancing metastasis by preventing the repressive interaction of p73 with the transcription factor NFY, thus increasing expression of the proinvasive PDGFRβ factor.[54]

Interacting with chromatin-associated proteins, mutp53 can affect gene expression and genome stability

P53 mutants can perturb the DNA-damage response and promote breast cancer cell survival also by interacting with nuclear proteins that are not sequence-specific transcription factors. One noticeable example is the interaction of mutp53 with the nuclease Mre11. By introducing two different mutations into a humanized p53 allele in mice, it has been demonstrated that high levels of mutp53 protein disrupt formation of the Mre11–Rad50–NBS1 complex at DNA double-strand breaks, leading to impaired ATM function and accumulation of mutations during proliferation of tumor cells.[55,56] Accordingly, an increased number of chromosomal abnormalities have been observed in breast cancers bearing p53 mutations.[57,58]

Another mutp53 GOF involves direct binding of mutp53 with the SWI–SNF chromatin-remodeling complex, observed in human breast cancer cell lines; via this interaction, hotspot p53 mutants might affect chromatin status and gene transcription in breast cancer.[59] The SWI–SNF complex associates genome-wide with transcription-regulatory elements to modulate nucleosome occupancy.[60] Although the authors have only explored the impact of SWI–SNF–mutp53 interaction in potentiating VEGFR2 signaling, SWI/SNF function is required at multiple mutp53 target genes, suggesting a more general role of this complex in mutp53-dependent gene regulation.[59]

In conclusion, although further studies are required to support this concept, p53 mutants may be linked to the control of chromatin status and structure, thus affecting the gene-expression profile of the cancer cell on multiple levels. This could explain why so many genes in tumor cells can be affected by the presence of p53 mutations, although the precise mechanism for this activity remains to be defined.

By forming complexes with cytoplasmic proteins involved in signal transduction, mutp53 alters the response of cancer cells to extracellular or intracellular inputs

Cytoplasm is where different signals are integrated, attenuated, or amplified, and where signaling pathways can talk to each other. Some of the GOF activities of mutp53 are mediated by its ability to form aberrant complexes with proteins not involved in gene transcription. Particularly interesting is mutp53 binding with cytoplasmic mediators of signal transduction.

For instance, mutp53 can bind the tumor suppressor DAB2IP in the cytoplasm of human breast cancer cells. DAB2IP is a cytoplasmic Ras GTPase-activating protein that also functions as a signaling scaffold to control the cell's responses to multiple signals.[61] The direct binding with mutp53 proteins interferes with physiological DAB2IP interactions, reprogramming the cell's response to extrinsic inputs. The mutp53–DAB2IP complex facilitates breast cancer metastases promoted by inflammatory stimuli, reducing TNF-induced activation of the proapoptotic ASK1–JNK axis, thereby promoting activation of proinvasive NFκB transcription factor (Figure 2A).[62] Similarly, mutp53-mediated block of DAB2IP functions promotes insulin-induced activation of the PI3K–Akt pathway, enhancing cell proliferation and invasion in hormone-independent breast and prostate cancers (Figure 2B).[63] Given the broad impact of DAB2IP in modulating signal transduction, it is possible that the mutp53–DAB2IP complex may also drive the acquisition of an aggressive phenotype in cancer cells exposed to other microenvironmental stimuli.

Another example of a cytoplasmic GOF for mutp53, observed in head and neck tumors but also confirmed in breast cancer models, is represented by the cytoplasmic interaction between mutp53 and AMPK. AMPK is an important energy sensor that regulates the balance between anabolism and catabolism. Under energy-stress conditions, mutp53 preferentially binds the AMPKα subunit and inhibits AMPK

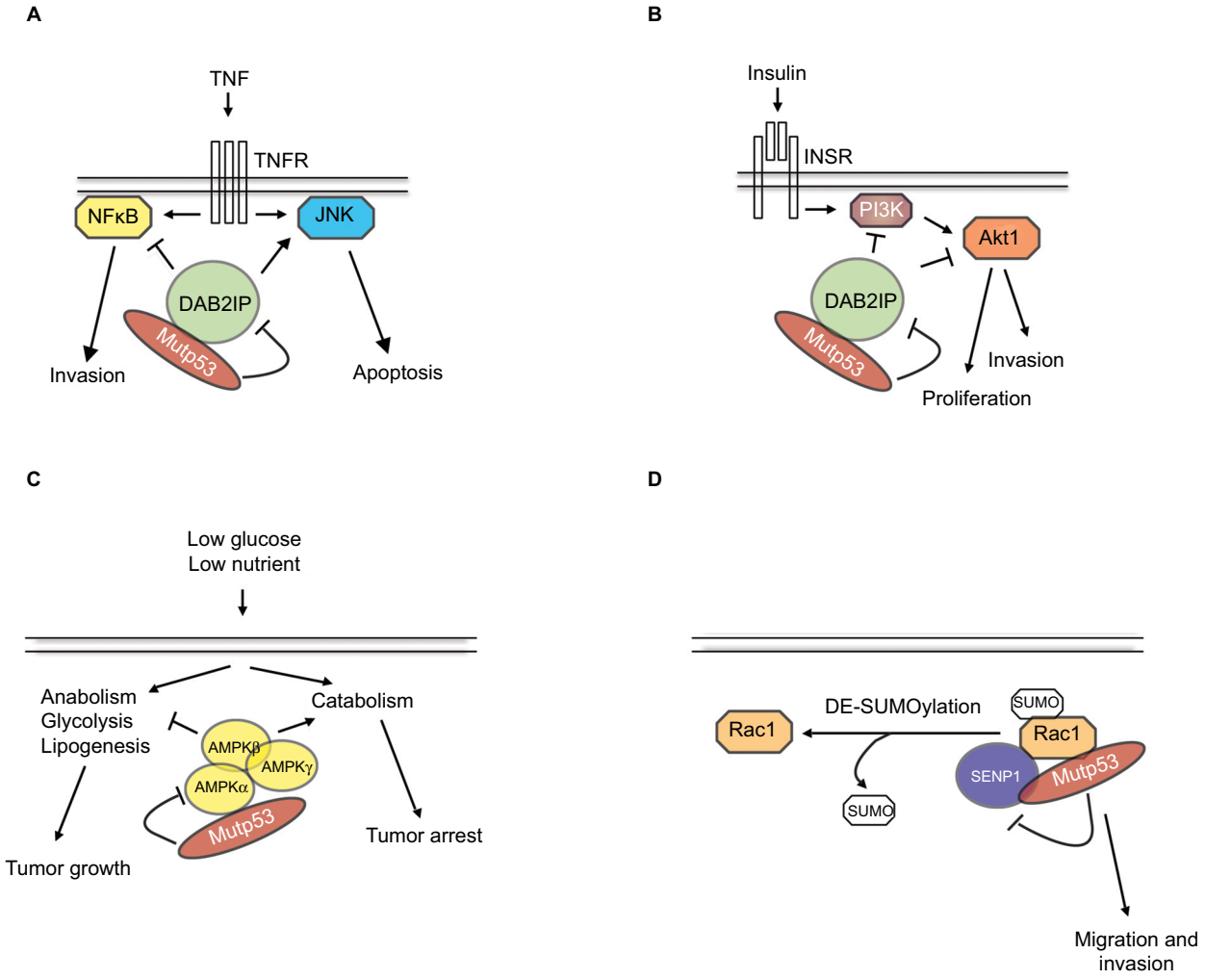

Figure 2 Mutant p53 (mutp53) forms complexes with cytoplasmic mediators of signal transduction.
Notes: (**A**) Mutp53 binds and inhibits the tumor suppressor DAB2IP in the cytoplasm of breast cancer cells, reducing TNF-induced activation of the proapoptotic ASK1–JNK axis, simultaneously promoting activation and of proinvasive NFκB transcription factor.[62] (**B**) Mutp53 inhibitory action on DAB2IP promotes insulin-induced activation of the PI3K–Akt pathway, enhancing cell proliferation and invasion in hormone-independent breast and prostate cancers.[63] (**C**) Mutp53 binds the AMPKα subunit and inhibits AMPK activation upon energy stress. This leads to increased anabolic growth of tumor cells and cancer progression.[64] (**D**) Mutp53 binds the monomeric GTPase Rac1, protecting it from SENP1-mediated de-SUMOylation. SUMOylated Rac1 is more active, sustaining tumor growth and dissemination.[65]

activation, thus leading to impaired metabolic checkpoint, increased anabolism, and consequent tumor growth and progression (Figure 2C).[64]

Very recently, Yue et al demonstrated that mutp53 can bind members of the monomeric GTPase family of proteins in the cytoplasm of multiple human cancer cell lines.[65] Specifically, mutp53 interacts with and activates Rac1, a small GTPase that regulates various cellular functions, including proliferation, cytoskeletal reorganization, and cell mobility. SUMOylation is critical to maintain Rac1 in an active GTP-bound form.[66] The sumo-specific protease SENP1 de-SUMOylates Rac1, leading to its inactivation.[67] Yue et al found that mutp53 interaction with Rac1 inhibited SENP1-mediated Rac1 de-SUMOylation, thereby promoting Rac1-dependent tumor growth and metastasis (Figure 2D).[65]

In conclusion, oncogenic conditions that lead to an increase in mutp53 protein levels also induce substantial cytoplasmic localization of the protein. It is legitimate to hypothesize that various nonphysiological protein interactions might occur in the cytoplasm, and the list of nontranscriptional complexes that may contribute to mutp53 GOF is likely to increase.

Complexes formed by mutp53 regulate its stability and functions

Factors that bind mutp53 may also promote its stabilization and activation, driving its oncogenic GOF. Consequently,

understanding such interactions could have important clinical implications.

Regulators of mutp53 stability

One important element of the oncogenic activity of mutp53 is its accumulation at significant levels in cancer cells. Interestingly, the majority of E3 ubiquitin ligases are shared between wild-type and mutp53; mutp53levels, in particular, are controlled through binding with Mdm2, CHIP, and Cop1.[68,69] It is believed that accumulation of high levels of mutp53 protein in cancer cells derives from an acquired capability to avoid E3-mediated ubiquitination. For example, mutp53 proteins are protected from degradation by the binding of cellular chaperones. HSP90 has been shown to protect mutp53 from both CHIP- and Mdm2-mediated ubiquitination.[70] Mutp53 forms a ternary complex with MDM2 and HSP90; upon DNA damage, MDM2 is released, but mutp53 is retained in the HSP90 complex and is protected from degradation.[71] Accordingly, destabilization of this complex favors mutp53 degradation and drug-induced cytotoxicity in tumor cells.[71–73]

Also, HSP70 binds mutp53 and partially inhibits Mdm2-driven ubiquitination.[74] In breast cancer cells and in mouse embryonic fibroblasts stably expressing exogenous human mutp53, elevated levels of HSP70 promote formation of nuclear HSP70 aggregates that include mutp53 and p73, limiting p73-dependent induction of apoptosis.[74] Analogously, BAG2 and BAG5 interact with mutp53 in breast and in other cancer cells, favoring accumulation of the mutp53 protein and the acquisition of oncogenic properties.[75,76]

Regulators of mutp53 activity

Research has suggested that mutp53 activity can also be modulated by posttranslational modifications. For instance, the transcriptional activity of mutp53 is potentiated by the action of Plk2. In human cell models, Plk2 binds and phosphorylates mutp53 in response to DNA damage, promoting formation of the p300–NFY–mutp53 complex on cell-cycle genes, thus favoring tumor progression and chemoresistance.[77] Intriguingly, mutp53 itself induces the transcription of Plk2, thereby potentiating this GOF circuit.[77]

Similarly, mutp53 function can be regulated by the prolyl isomerase Pin1. In breast cancer cells, Pin1-mediated isomerization enhances the oncogenic activity of mutp53, possibly by enhancing its interaction with TAp63, and drives expression of a mutp53-dependent transcriptional program that fosters cancer-cell proliferation and invasion.[45] Mutp53 oncogenic functions can also be regulated by Pontin, an AAA+ (adenosine triphosphatase associated with diverse cellular activities) ATPase involved in multiple biological processes, including cellular energetic metabolism, transcription, chromatin remodeling, and DNA-damage response.[78,79] The ATPase activity of Pontin promotes mutp53-mediated transcriptional upregulation of multiple genes involved in migration, invasion, and anchorage-independent growth of tumor cells.[79] There are some analogies between the action of Pin1 and Pontin on mutp53; the fact that they both require catalytic activity raises interesting possibilities to blunt mutp53 GOF by development of specific pharmacological inhibitors.

Therapeutic approaches targeting mutp53 protein complexes

As reviewed here, the oncogenic properties of mutp53 are tightly related to its ability to form complexes with other proteins. These can be downstream targets, directly or indirectly involved in DNA transcription or signal transduction, or can be upstream modulators, controlling mutp53 stability and activity. In any case, pharmacological approaches aimed at disrupting mutp53 complexes represent an appealing strategy for cancer therapy. Such approaches may operate along three possible lines of attack: stabilizing mutp53 structure to restore its wild-type functions, preventing or disrupting oncogenic complexes with specific target proteins, and reducing mutp53 levels by targeting the axis that determines its accumulation and activity (Figure 3).

A variety of compounds that elicit mutp53 destabilization, inactivation, or reactivation of wild-type p53 functions have been developed.[80] PRIMA-1 and its analogue PRIMA-1Met can refold various p53 mutants, restoring wild-type DNA binding and inducing apoptosis. PRIMA-1Met suppresses cancer progression in animal models and is currently undergoing clinical trials. Interestingly, other small molecules, such as RETRA and NSC59984, have been shown selectively to kill mutp53-bearing cancer cells in a p73-dependent manner: these molecules release p73 from the inhibitory interaction with mutp53, promoting drug-induced cell death.[53,81]

Another option is to try to disrupt complexes that are involved in mutp53 GOF. For instance, we used a chimeric "decoy" protein (GFP-KA2) to displace the mutp53–DAB2IP complex.[62] Expression of such a decoy abolished inflammation-driven invasion in vitro and xenograft growth and dissemination in breast cancer cell models.[62] Similarly, expression of the GFP-KA2 decoy blocked insulin-induced proliferation and invasion in breast cancer cells.[63] These results provided a proof of principle that peptide or nucleotide aptamers designed to interfere with aberrant complexes

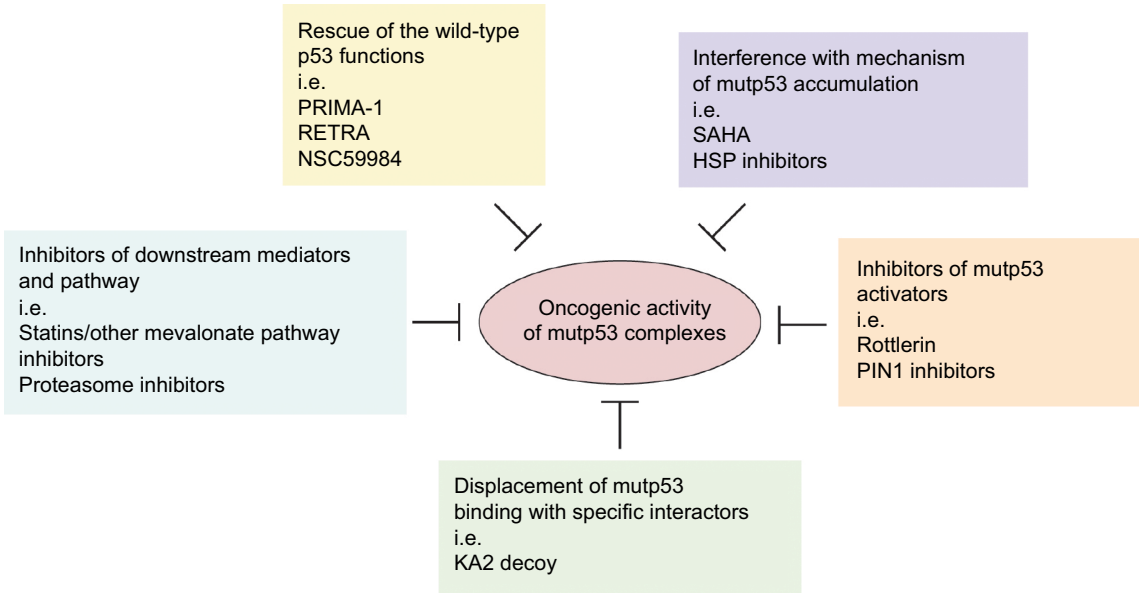

Figure 3 Therapeutic approaches targeting mutant p53 (mutp53) protein complexes.
Notes: Pharmacological approaches aimed at disrupting mutp53 complexes represent an appealing strategy for cancer therapy. Such approaches involve stabilizing mutp53 to restore its wild-type functions, reducing mutp53 levels by disrupting mechanisms of mutp53 accumulation, counteracting mutp53 activity by targeting specific mutp53 modulators, preventing or disrupting oncogenic complexes with specific target proteins, and inhibiting mediators or pathways downstream of mutp53 protein complexes (see text for details).

formed by mutp53 may have a putative application in targeted therapy of breast cancer malignancy. With the same logic, tools designed to prevent mutp53 interaction with crucial transcriptional partners, such as NFY, SP1, TAp63, and p73, would have useful applications in limiting cancer progression.

Other possible approaches aimed at destabilizing mutp53 protein complexes involve disruption of mechanisms that promote mutp53 stability and activity. For instance, blocking the function of HSP90 via 17-AAG or ganetespib promotes degradation of p53 mutants, favoring apoptosis induction in in vivo tumor models.[70,82] Ganetespib efficiency is under evaluation in clinical trials, with promising results, especially in lung carcinoma and in metastatic breast cancer.[83,84] Similarly, SAHA, a histone deacetylase inhibitor, stimulates degradation of mutp53 by inhibiting HDAC6, a key positive regulator of HSP90. SAHA treatment disrupts HDAC6–HSP90–mutp53 complexes, leading to mutp53 ubiquitination via MDM2 and CHIP.[73] Recently, Wang et al demonstrated that in TNBC, SAHA specifically reduces the transcription of mutp53 by blocking the activity of the HDAC8–YY1 protein complex, with higher cytotoxic effect in cancer cells bearing p53 mutations with respect to those with wild-type or null p53.[85]

The Pontin-specific ATPase inhibitor rottlerin also gave efficient results on mutp53-bearing tumors, reducing cell migration, proliferation, and expression of oncogenic mutp53-target genes.[79] Similarly, destabilization of mutp53/Pin1 oncogenic functions by the employment of specific Pin1 inhibitors showed powerful tumor suppression in breast cancer preclinical models.[86]

Finally, knowledge of the molecular circuits at the base of mutp53 GOF may suggest possible lines of intervention that combine drugs targeting mutp53 with drugs targeting related molecular pathways. One such example is the mutp53–Nrf2 complex that drives expression of proteasome subunits, increasing protein turnover in breast cancer cells.[30] In this model, combination of the mutp53-inactivating agent PRIMA-1Met with the proteasome inhibitor carfilzomib showed high efficacy in reducing primary tumor growth and dissemination in mammary fat-pad xenografts.[30] Another example is provided by the SREBP2–mutp53 complex and regulation of mutp53 levels by the mevalonate pathway. In fact, treatment with statins, compounds that inhibit HMG-CoA reductase, induce mutp53 degradation and loss of function. Accordingly, statins suppress progression of mammary tumors bearing p53 mutations in preclinical models.[27,28,87]

In conclusion, a detailed understanding of the transcriptional and nontranscriptional complexes involving mutp53 is an important prerequisite for the development of novel molecules to target mutp53 oncogenic functions, as well as for effective repurposing of existing drugs that may be employed to target these complexes or their related pathways. Together,

these approaches may develop into novel therapeutic strategies for the treatment of tumors bearing mutp53.

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Disclosure

The authors report no conflicts of interest in this work.

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