Review Article

# Modulation of the p53 family network by RNA-binding proteins

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**Abstract:** Since its discovery more than three decades ago, tumor suppressor p53 has been shown to play pivotal roles in both maintaining genomic integrity and tumor suppression. p53 functions as a transcription factor responding to a multitude of cellular stressors, regulating the transcription of many genes involved in cell-cycle arrest, senescence, autophagy, and apoptosis. Extensive work has revealed that p53 is one of the most commonly mutated tumor suppressor genes. The last three decades have demonstrated that p53 activity is controlled through transcriptional regulation and posttranslational modifications. However, evolving work is now uncovering that p53, and other p53 family members, are post-transcriptionally regulated by multiple RNA-binding proteins (RBPs). Understanding the regulation of p53 by RBPs may potentially open up the possibility for cancer therapeutic intervention. This review focuses on the posttranscriptional regulation of p53, and p53 family members, by RNA binding proteins and the reciprocal feedback pathways between several RNA-biding proteins modulating p53, and p53 family members.

**Keywords:** Rbm38; p53; RNA-binding proteins (RBPs); post-transcriptional regulation

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## Introduction

It is fundamentally understood that the differential expression of a distinct assemblage of proteins is attributed to cancer cells' ability to develop, proliferate, and metastasize (1). Indeed, increasing evidence has revealed that deregulated protein synthesis plays a critical role in cell transformation (2-4). Irregular protein expression may not only be due to gene mutations and altered transcription, but also through transformed posttranscriptional machineries such as mRNA storage, transport, splicing, translation, and degradation (5-8). These aforementioned mechanisms are directed by two distinct RNA-binding factors; microRNAs and RNA-binding proteins (RBPs) (9). While both microRNA and RBPs play a role in posttranscriptional regulation, the focus of this review is on the current understanding of RBP regulation of p53, p53 family members, and p53 downstream targets. For a detailed review on p53 regulation by microRNA please see (10). Multiple cancer related proteins, including tumor suppressors and oncoproteins, are tightly controlled through translational regulation and/or mRNA half-life, emphasizing the influence of RBPs on the expression of cancer associated proteins (5,11). Translation, as well as mRNA decay, is typically influenced by RBPs interacting with target gene transcripts. Characteristically, the sequences in the mRNA that modulate translation and mRNA stability usually reside in the 5'- and 3'-untranslated regions (UTRs).

Structurally, RBPs possess a high proportion of modularity, as seen by the majority of RBPs containing at least one or more RNA-binding and auxiliary domains (12). The differential combination and arrangements of these RNA-binding modules assist in the numerous interactions

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and regulatory abilities of these RBPs [reviewed here (13)]. To date, numerous classes of RNA-binding motifs have been identified including, RNA recognition motif (RRM), hnRNP K homology (KH) motif, RGG box, Pumilio, and double-stranded RNA-binding motif (13,14). Since many disease associated proteins are subjected to rigorous posttranscriptional regulation, it is without surprise that aberrant expression of RBPs have been tied to several human diseases including, neurological disorders, muscle atrophies, and cancer (11,15). Numerous RBPs have been linked with tumorigenesis (7). For example, aberrant eIF4E (eukaryotic translation initiation factor 4E) expression has been shown to lead to malignant transformation in mouse and rat fibroblasts (16), and further, targeting eIF4E with a cell-penetrating peptide leads to cell death in multiple cancer cell lines (17). Another important RBP in cancer, human antigen R (HuR), was one of the earliest RBPs identified to be aberrantly expressed in human malignances, including mammary and colon cancers (18,19). Extensive studies over the past decade revealed that HuR has the ability to induce the stability of many cancer-related transcripts including cytokines, growth factors, invasion factors, and other proto-oncogenes [for a review of HuR in cancer please see (20)]. Collectively, various lines of evidence have come to light establishing that posttranscriptional regulation by RBPs may play a role in multiple human diseases including cancer.

## Regulation of p53

p53 is a transcription factor with an essential role in conserving the overall integrity of the genome and aiding in the prevention of cancer development. Highlighting the necessity for p53 in inhibiting tumorigenesis is the evidence that p53 inactivation occurs in more than 50% of human cancers (21). Under normal circumstances, p53 is highly regulated and protein expression is kept at low levels. However, in reaction to stress stimuli, p53 is activated and functions as a robust transcription factor inducing the activation of downstream targets that function in DNA repair, cell-cycle arrest and apoptosis (22-24). The importance of strict p53 protein regulation is underscored by the fact that too much p53 leads to premature ageing (25) and cell death due to excessive apoptosis (26), whereas too little p53 has been shown to be a key aspect of tumorigenesis (27).

Most work on the regulation of p53 has been demonstrated to be through posttranslational modifications, such as acetylation and phosphorylation. For example, phosphorylation of p53's Ser15 (mouse Ser18) and Ser20 (mouse Ser23) at its N-terminus is believed to stabilize p53 by blocking its interactions with a key p53 inhibitor, MDM2 (28). Furthermore, in response to stress stimuli, p53 acquires increased acetylation correlating with increased p53 stabilization and activation (29-31). Subsequent studies revealed that not only were acetylation and phosphorylation important for regulating p53 stability and function, but other posttranslational modifications such as methylation, sumoylation, neddylation and ubiquitination were also able to modulate p53's function and stability (32). Besides posttranslational modifications, it is now starting to be understood that p53 is also regulated through posttranscriptional mechanisms.

To date, multiple RBPs have been found to regulate p53 translation by interacting with the 5' or 3' UTR of p53 mRNA. An RBP extensively studied in our laboratory, RBM38, also known as RNPC1, was determined to be a target of p53, and a key regulator of p53 expression. Over-expression of RBM38 inhibits, while knockdown of RBM38 increases, p53 translation in both basal and stress conditions (33). The inhibition of p53 translation was attributed to RBM38 interacting with p53 5' and 3' UTRs. Upon binding to p53 mRNA, RBM38 is able to interact with eIF4E. As an essential component of mammalian translation, eIF4E binds to the 5' mRNA cap leading to the start of translation. The physical interaction between RBM38 and eIF4E causes the dissociation of eIF4E from p53 5' UTR, subsequently leading to decreased p53 translation. Furthermore, we demonstrated that phosphorylation of RBM38 at Ser195 modulates its ability to regulate p53 translation (*Figure 1A*). RBM38 phosphorylation by glycogen synthase kinase 3 (GSK3) enhances p53 translation by removing the RBM38 interaction with eIF4E, inducing p53 translation (34). Additionally, PPM1D phosphatase, a target of both p53 and RBM38, causes decreased phosphorylation of RBM38 at Ser195 leading to decreased p53 translation, as represented in *Figure 1A* (35). Physiologically, loss of RBM38 in mouse embryonic fibroblasts increased p53 protein levels triggering elevated premature senescence (36). RBM38 was additionally shown to be frequently elevated in dog lymphomas, often correlating with decreased expression of wild-type p53, emphasizing a novel auto-regulatory loop between p53 and a target RBP. The RBM38-p53 axis is not the only p53 target RBP autoregulation discovered thus far. For example, wild-type p53 induced gene 1 (WIG-1), a known p53 target and double-stranded-RNA-binding

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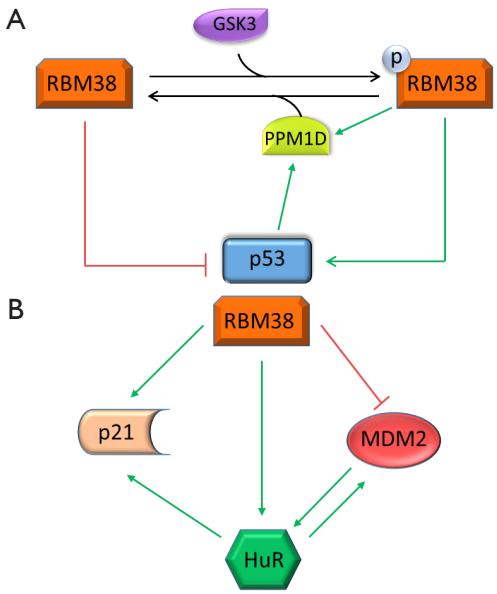


**Figure 1** Multiple mechanisms of regulating the p53 network by RBM38. (A) Phosphorylation of RBM38 by GSK3 leads to increased p53 translation, whereas dephosphorylation of RBM38 by PPM1D causes decreased p53 translation; (B) RBM38 and HuR work together to increase p21 expression via mRNA stability. MDM2 mRNA stability is increased by HuR but decreased by RBM38. GSK3, glycogen synthase kinase 3; HuR, human antigen R.

zinc finger protein, was shown to stabilize p53 mRNA by interacting with an AU-rich element (ARE) in p53 3' UTR leading to increased p53 expression in both normal and stressed cells (37).

Besides RBM38, various other RBPs have been revealed to regulate p53 translation. For example, ribosomal protein L26 (RPL26) augments p53 translation after DNA damage by interacting with a stem loop formed by p53 5' and 3' UTRs. RPL26 binding to p53 mRNA leads to an enhanced association with heavier polysomes, ultimately increasing p53 translation. The increased p53 translation results in G1 cell-cycle arrest and heightened irradiation-induced apoptosis (38). Another RBP, polypyrimidine tract-binding protein (PTB), a p53 internal ribosome entry site (IRES) interacting trans-acting factor, differentially controls the expression of p53 isoforms by preferentially binding to both p53 IRES elements (39). Moreover, HuR binds to target mRNAs with AREs and has been shown to modulate p53 translation via multiple approaches. HuR enhanced p53 translation in RKO cells treated with UVC by binding to the 3' UTR of p53 mRNA, whereas decreased HuR protein levels reduced p53 translation (40). Alternatively, HuR was demonstrated to induce p53 translation via von Hippel-Lindau (VHL)-dependent binding to p53 3' UTR (41), and further, in polyamine-depleted intestinal epithelial cells, HuR enhanced p53 mRNA stability (42). The above mentioned studies highlight the intricacy of HuR-mediated p53 expression. Like RBM38, other RBPs have been shown to inhibit p53 translation. For example, nucleolin competes with RPL26 to bind to p53 mRNA leading to decreased p53 translation. Over-expression of nucleolin subdued, whereas reduced endogenous nucleolin levels enhanced, IR-mediated p53 translation (38). Furthermore, thymidylate synthase binds to the C-terminal coding region of p53 mRNA leading to suppressed p53 translation (43). Interestingly, our laboratory recently demonstrated that PCBP4, a KH domain containing RBP and target of p53 (44), indirectly regulates p53 protein levels by modulating the mRNA stability of ZNF709. Knockout of PCBP4 led to increased ZNF709 protein expression ultimately leading to decreased p53 via a proteasome-dependent degradation pathway (45). These lines of evidence further solidify the overwhelming complexity of p53 regulation and open up the possibility for potential therapeutic intervention by modulating the regulation of p53 by RBP's.

## Regulation of p53 family member's p63 and p73

Years after the discovery of p53, two highly homologous p53 family members were discovered, p63 and p73. With the discovery of p63 in 1997, and p73 in 1998, initial thoughts were that these two family members may share similar tumor suppressor functions to p53 (46-49). However, while p63 harbors many p53-like attributes, such as inducing cell-cycle arrest, senescence and apoptosis, p63 is not a classic tumor suppresser, but rather, has been shown to be critical for proper development (50,51). Of interest, p63 is expressed as two isoforms, TAp63 and ΔNp63. Subsequent studies have demonstrated that TAp63 may function as a tumor suppressor promoting cell cycle arrest, senescence, and apoptosis (52). However, ΔNp63 acts as an oncogene, with the ability to bind p53-responisve promoters, leading to repressed gene expression of p53 targets (53). Further, ΔNp63α is frequently over-expressed in low-grade squamous cell carcinomas mostly attributed to chromosomal amplification (54). Likewise, p73 is expressed as two isoforms, TAp73 and ΔNp73. TAp73 functions as a tumor suppressor capable of inducing apoptosis and cell cycle arrest. Similar to ΔNp63, ΔNp73 may act as an oncogene inhibiting both TAp73 and p53 functions (55).

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Captivatingly, our group uncovered that RBM38 negatively regulates p63 mRNA stability by interacting with AU-/U-rich elements in p63 3' UTR (56). In addition, our laboratory recently discovered that RBM24, which has high sequence homology to RBM38 (57), was able to bind multiple regions in p63 3' UTR, subsequently destabilizing the p63 transcript, leading to decreased p63 protein expression (58). Contrastingly, it was revealed that PCBP1 positively regulates p63 transcript by interacting with a CU-rich element (CUE) in p63 3' UTR leading to increased p63 mRNA and protein levels (59). The p53 family member p73 is likewise regulated by multiple RBPs. For example, PCBP2 interacts with CUEs in p73 3' UTR causing increased p73 mRNA stability and increased protein expression (60). Of interest, RBM38 was also shown to be a p73 target, and capable of binding a CUE in p73 3' UTR leading to enhanced p73 mRNA stability, emphasizing a novel positive feedback regulation between the two genes (61). Underlining the complex regulation of p53 family members by RBPs is demonstrated by the ability for RBM38 to decrease p53 mRNA translation, inhibit p63 expression via destabilization of its transcript, and promote p73 expression by increasing its mRNA stability.

## Regulation of MDM2

As a key regulator and downstream target of p53, MDM2 was first identified as having gene amplification on double-minute chromosomes in transformed mouse fibroblasts (62). Further studies soon discovered that MDM2 was overexpressed in multiple human cancers, such as soft tissue sarcomas and osteosarcomas (63-65). Interestingly, high expression levels of MDM2 has been correlated with increased genomic instability revealed by amplified chromosome breaks, aneuploidy or polyploidy (66). Importantly, MDM2 interacts with p53 forming a regulatory feedback loop, where p53 induces MDM2 expression, and MDM2 negatively regulates p53 function and protein levels (67). MDM2 has been demonstrated to repress p53 transcriptional activity and lead to p53 protein degradation through three modes of action: (I) conceal the p53 transactivation domain; (II) cause the shuttling of p53 out of the nucleus; (III) target p53 for degradation as an E3 ubiquitin ligase (68-71).

A substantial amount of work has been done to unravel the regulatory mechanisms leading to increased MDM2 expression in cancer cells. In addition to the regulation by p53, multiple cancer cell lines exhibit enhanced MDM2 protein translation, such as cutaneous melanoma cells, breast cancer cells, and Burkitt's lymphoma, underlining one potential mechanism for increased MDM2 protein levels (72-74). MDM2 transcription is under the control of two distinct promoters, P1 and P2 (75,76). Eloquent studies demonstrated that the P1 promoter, upstream of the first exon is responsible for the control of the basal expression of MDM2, whereas the P2 promoter located in the first intron is responsible for the inducible expression of MDM2. While both promoters encode identical transcripts, the translation efficiency due to differences in their 5' UTR is where they differ. The transcript from the P1 promoter contains two upstream open reading frames and was shown to have lower translation efficacy. Contrastingly, the 5' UTR from the P2 promoter was determined to be shorter allowing for efficient translation (75,76). Further, the Ras-driven Raf/MEK/MAP kinase pathway was discovered to induce MDM2 in a p53-independent fashion via activation of Ets and AP-1 sites in the P2 promoter (77).

MDM2 is also post-transcriptionally regulated by multiple RBPs. For example, our laboratory has reported that RBM38 influences MDM2 post-transcriptionally. Overexpression of RBM38 led to decreased MDM2 transcript and protein levels independent of p53 as represented in *Figure 1B* (78). This regulation was determined to be the result of RBM38 destabilizing MDM2 mRNA by binding to multiple AU-/U-rich elements in MDM2 3' UTR. With interest, HuR was discovered to be able to interact with, and stabilize, MDM2 mRNA (79). In addition, HuR is positively regulated by RBM38 via mRNA stability (80). Added, in a regulatory feedback loop, MDM2 interacts with, and stabilizes, HuR via MDM2-mediated NEDDylation, sequestering HuR in the nucleus protecting HuR from degradation (81). Both HuR and MDM2 contrastingly regulate p53, and stabilize each other, adding further complexity to the p53 regulation by RBPs. Further, BCR/ABL-expressing myeloid precursor cells showed enhanced MDM2 mRNA translation that required the interaction of the LA antigen with a 27-nucleotide segment in MDM2 5' UTR. Suppressing La by siRNA resulted in decreased MDM2 expression and heightened susceptibility to drug-induced apoptosis (82). Additionally, extensive work has revealed that numerous ribosomal proteins regulate MDM2, thus modulating p53 proteins levels (83). This intricate network of regulatory feedback between p53 and p53 targets with RBPs becomes more apparent as shown by the aforementioned regulations of the RBM38/MDM2/HuR/p53 axis.

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## Regulation of p21

A number of p53 targets are implicated in inhibiting tumorigenesis. For example, p21, a key regulator of p53 involved in cell cycle arrest, belongs to the Cip and Kip family of cyclin-dependent kinases (CDK) inhibitors. As a CDK inhibitor, p21 was discovered to be a major regulator in cell cycle transition from G1 to S by inhibiting the kinase activity of CDK2 and CDK1 (also known as CDC2) (84). Further, p21 directly interacts with proliferating cell nuclear antigen (PCNA), leading to decreased PCNA-dependent DNA polymerase activity, consequently inhibiting DNA replication and adversely affecting other PCNA-dependent DNA repair processes (85,86). Interestingly, p21 was shown to be a master regulator of multiple tumor suppressor pathways that were revealed to be independent of the p53 tumor suppressor pathway (87).

In addition to the regulation by the p53 family, p21 is regulated by multiple p53-independent mechanisms (46,50,84,88) [for a comprehensive review please see (89)]. For example, the signaling through the Ras GTPase induces, whereas signaling through the Rho GTPase inhibits, p21 transcription (90). This transactivation of p21 through Ras signaling was later revealed to require the transcription factor E2F1 (91). Heterogeneous nuclear ribonucleoprotein K (hnRNP K) was also shown to specifically bind to CUEs in p21 3' UTR leading to p21 translational repression (92). Like p53, p21 is positivity regulated by HuR. HuR interacts with the 3' UTR of p21 mRNA causing increased inducibility and half-life of the p21 transcript (93). Further, RBM38 stabilizes both the basal and stress-induced p21 transcripts by directly binding to the 3' UTR of p21 mRNA (94). Increasing the complexity of p21 regulation by RBM38, it was later discovered that RBM38 and HuR physically interact and preferentially bind the upstream and downstream AREs in p21 3' UTR, respectively (95). Additionally, the RNA-binding activity of HuR to the p21 transcript was enhanced with increased RBM38 protein expression, suggestion a cooperative regulation of p21 by both RBPs as demonstrated in *Figure 1B*. Our group additionally established that RBM24 was able to interact with an AU/U rich region located in p21 3' UTR heightening p21 expression (57). PCBP1 and PCBP2 have also been revealed to cause decreased p21 mRNA stability via interaction with its 3' UTR (96). Moreover, PCBP4 was proven by our group to negatively regulate the p21 transcript. In PCBP4-deficient mice, it was discovered that p21 expression was noticeably enhanced, and this regulation by PCBP4 was due to its binding to p21 3' UTR, negatively regulating p21 mRNA stability (97). Collectively, the reciprocal regulation of p53, and p53 targets, by RBPs is indeed complex. Recapitulated by the p53/HuR/RBM38/p21 regulatory axis, this adds further credence for the additional study of the posttranscriptional regulation of p53 and downstream targets by RBPs.

## Conclusions and perspectives

In light of recent works, the significance of gene regulation via posttranscriptional regulation has been revealed to not only regulate p53, but that of p53 family members and downstream targets. Until recently, most emphasis has been put towards understanding the transcriptional and posttranslational modifications dictating p53 function and downstream pathways. However, as highlighted in this review, an increased understanding of the posttranscriptional regulation of p53 and p53 targets will surely be needed to appreciate the role of p53 in tumor suppression, and subsequently, in the development of p53-based therapies. Herein, we reiterated the ability for multiple RBPs to regulate p53, and p53 pathways. While it is now understood that p53 and p53 targets are regulated by RBPs, the reciprocal regulation of these RBPs in a regulatory feed-back loop with p53 is just now starting to be revealed.

Even though the last 30 years of research have uncovered an enormous amount of detail about the biology of p53, nonetheless, numerous questions about p53 regulation continually reappear in a new context. With the exciting findings of the reciprocal regulation of p53 by RBPs, such as the RBM38/HuR/MDM2/p53 regulatory loop, our knowledge of the complex regulation of p53 and the p53 network allows for the potential intervention with therapeutic approaches to upregulate the expression of p53, or p53 targets like p21. For example, as depicted in *Figure 1*, the regulatory network by RBM38 is multifaceted. RBM38 is induced by p53 and negatively effects p53 translation, while also adversely affecting MDM2, a key regulator of p53. Further, HuR upregulates p53, but also increases MDM2 translation. In addition, RBM38 and HuR cooperatively influence p21 mRNA stability increasing its expression. One could imagine, with a therapeutic application, that by removing the inhibition of RBM38 on p53, this would lead to an increase in both p53 and p21, potentially inducing tumor suppression. Blocking RBM38 from binding to p53 mRNA using oligonucleotides, or inhibiting the interaction between RBM38 and eIF4E via small

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competing peptides are two possible approaches aimed at modulating RBM38 regulation of p53. Importantly, RBM38 deficiency was shown to decrease tumor penetrance in mice heterozygous for p53 by enhancing p53 expression (36). Accumulating research into RBPs is continually revealing new RBPs and targets, while many questions still remain unanswered. For example, with increasing evidence that multiple RBPs are capable of regulating a single target, how is this regulation synchronized? Further, is there a reciprocal coordination between p53 and RBPs to regulate mutual targets, such as p21 or MDM2? Nonetheless, additional work is needed to garnish the knowledge of the intricate regulation of p53 and p53 family members with the hope of devising potential therapeutic approaches targeting RBPs.

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