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Posttranscriptional Regulation of p53 and Its Targets by RNA-Binding Proteins

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Abstract

p53 tumor suppressor plays a pivotal role in maintaining genomic integrity and preventing cancer development. The importance of p53 in tumor suppression is illustrated by the observation that about 50% human tumor cells have a dysfunctional p53 pathway. Although it has been well accepted that the activity of p53 is mainly controlled through post-translational modifications, recent studies have revealed that posttranscriptional regulations of p53 by various RNA-binding proteins also play a crucial role in modulating p53 activity and its downstream targets.

Keywords

p53; posttranscriptional regulation; RNA-binding proteins; translational regulation; mRNA decay

Introduction

It is becoming increasingly appreciated that posttranscriptional regulations of gene expression, such as mRNA decay and translation, play a critical role in regulating gene expression. In support of this notion, a growing body of evidence suggests that deregulated protein synthesis plays an important role in cell transformation [1-4]. Regulation of mRNA decay or translation is mainly controlled by the interaction of a particular sequence in an mRNA with RNA-binding proteins (RBPs). RBPs generally contain one or more RNA-binding domains along with auxiliary domains for protein-protein interaction and subcellular targeting [5]. There are four major classes of RNA-binding motifs, including RNA recognition motif (RRM), hnRNP K homology (KH) motif, RGG box, and double-stranded RNA-binding motif (dsRBD) [6,7]. Given the important biological function of RBPs, it is conceivable that altered expression of RBPs has a profound effect on cell cycle progression, cell survival and cell death. Indeed, over-expression of various RBPs was found in several human diseases. For example, aberrant HuR (Hu antigen R) expression was detected in colon and mammary cancers [8,9]. In addition, altered expression of RBPs was found in a variety of genetic disorders, such as fragile X mental retardation and myotonic dystrophy [4].

The p53 tumor suppressor plays a pivotal role in preserving the integrity of the genome and preventing cancer development. The importance of p53 in this process is demonstrated by the fact that inactivation of p53 tumor suppressor occurs in over 50% of human cancer and loss of p53 function is known to play a central role in cancer development [10]. p53 protein is expressed at low levels under unperturbed conditions. In response to a stress signal, p53 is activated and functions as a transcriptional factor to activate its downstream targets, which are

involved in cell cycle arrest and apoptosis [11,12]. Therefore, p53 and its downstream targets form a network, where p53 is a key molecular node in the network.

In vitro studies showed that the activity of p53 is mainly controlled through posttranslational modifications, including phosphorylation and acetylation. For example, phosphorylation of human p53 at serine 15 (S15) was reported to be responsible for p53 stabilization in response to IR [13]. Similarly, serine 20, which lies in a region required for MDM2-mediated p53 degradation, was shown to be critical for stabilizing p53 after DNA damage [14,15]. Intriguingly, *in vivo* studies from knock-in mice, which carry mutation of Ser18 (corresponding to Ser15 in the humans) or Ser23 (corresponding to Ser20 in the humans), revealed that mutation of these amino acids does not have any significant effect on the stability of either basal or DNA damage-induced p53 protein levels [16-19]. This suggests that in addition to these modifications, other mechanisms may play a role in modulating p53 activity *in vivo*. Indeed, evidence has emerged that posttranscriptional regulations of p53 by various RBPs are critical for modulating p53 activity and thereby the p53 network. Here, we will focus on the regulation of p53 and its targets by RBPs, and how such a regulation might be explored for cancer therapeutics.

Regulation of p53

The first evidence that p53 expression might be translationally regulated was reported in 1984 [20]. The study showed that the rate of p53 protein synthesis is increased in UV-treated cells as measured by [³⁵S]methionine metabolic labeling assay [20]. In line with this, several other groups have reported that protein synthesis inhibitors, such as cycloheximide, prevent p53 accumulation in response to DNA damage [21-24].

The p53 mRNA is predicted to contain a highly ordered secondary structure and is likely subject to translational control. Consistent with this, several regulatory elements have been identified in both the 5' and 3' UTR in the p53 mRNA. Specifically, the 3' UTR of human p53 mRNA contains a 66-nt U-rich sequence, which is responsible for translational repression of p53 mRNA *in vitro* and *in vivo* [25,26]. Likewise, murine p53 represses its own translation via binding to a stem-loop structure in the 5' UTR of murine p53 mRNA [27]. Recently, two studies have revealed that the 5' UTR in human p53 mRNA contains an internal ribosome entry site (IRES). In one study, two IRESs (one from nt -134 to +1 and the other from nt -134 to +39) were found in the 5' UTR of p53 mRNA, both of which are capable of translating the full-length and ΔN p53 isoforms in a cell cycle-dependent manner [28]. In the other study, one IRES element (from nt -131 to -1) was identified in the p53 mRNA [24]. In addition, the study showed that the activity of the IRES element was increased in MCF7 cells treated with DNA damaging agent etoposide, which is accompanied with increased p53 translation [24]. These data suggest that IRES-mediated protein translation may play a role in p53 accumulation upon DNA damage.

Thus far, several RBPs have been found to promote p53 translation through binding to the 5' or 3' UTR of p53 mRNA. For example, HuR, a RBP that belongs to the embryonic lethal abnormal visual (ELAV) family and preferentially targets mRNAs with AU-rich elements (AREs), was shown to enhance p53 translation by directly binding to the 3' UTR of p53 mRNA in RKO cells exposed to UVC [29]. Consequently, over-expression of HuR in RKO cells elevated p53 levels, while targeting endogenous HuR markedly diminished p53 translation [29]. Likewise, HuR was found to enhance von Hippel-Lindau (VHL)-mediated p53 translation by binding to the 3' UTR of p53 mRNA in the renal carcinoma cells [30]. The regulation of p53 by HuR was found through enhanced mRNA stability in polyamine-depleted intestinal epithelial cells [31]. Therefore, HuR-mediated p53 expression is complex and may be cell type-specific. Like HuR, Ribosomal Protein L26 (RPL26) was found to enhance p53 translation by

preferentially binding to the 5' UTR of p53 mRNA after DNA damage, thereby enhancing p53-mediated G1 arrest and apoptosis [32]. Conversely, targeting RPL26 was shown to attenuate p53 translation. Furthermore, Unr (upstream of N-ras), a cytoplasmic RBP known to be involved in regulating IRES-mediated protein translation, was found to be required for p53 stabilization in ES cells although the mechanism is not clear [33].

In addition to promote p53 translation, several RBPs were found to inhibit p53 translation. For instance, thymidylate synthase, a folate-dependent enzyme with a RNA-binding domain, is capable of binding to the C-terminal coding region of p53 mRNA and repressing p53 translation. Over-expression of thymidylate synthase was found to significantly reduce the level of p53 protein but not mRNA, and consequently impair the ability of gamma irradiation-induced G1 arrest in HCT-C18 cells [34,35]. Similarly, nucleolin, a RBP critical for precursor rRNA (pre-rRNA) processing [36], was found to inhibit p53 translation by competing with RPL26 to bind to the 5' UTR of p53 mRNA [32]. Over-expression of nucleolin in MCF7 cells inhibited, while targeting endogenous nucleolin enhanced, IR-mediated p53 translation. In addition, p53 was found to interact with nucleolin and guide its translocation from nucleolus to nucleoplasm in response to DNA damage, which plays a role in DNA repair and transient inhibition of DNA replication [37]. This suggests that in response to a stress signal, p53 and nucleolin may regulate each other. In *C. elegans*, the p53 homolog cep-1 was found to be translationally inhibited by RNA-binding protein GLD-1 [38]. Specifically, wild-type GLD-1 was found to bind to the 3' UTR of cep-1 mRNA and repress cep-1 translation and its transcriptional activity. In line with this, over-expression of mutant GLD-1(V276F) was shown to enhance p53-mediated germ cell apoptosis in response to DNA damage.

Regulation of MDM2

The murine double minute-2 (MDM2) proto-oncogene was originally isolated by virtue of its amplification in a tumorigenic derivative of NIH-3T3 cells [39,40]. Shortly after its discovery, MDM2 was found to be over-expressed in various human cancers, such as osteosarcomas and soft tissue sarcomas [41-43]. MDM2 functions as an E3 ubiquitin ligase and activates degradation of p53 [44,45]. In human and murine tissues, MDM2 and p53 form a regulatory feedback loop, with p53 activating MDM2 expression and MDM2 degrading p53 [46]. The importance of MDM2 in controlling the p53 activity is demonstrated in MDM2 knockout mice. MDM2-null embryos die very early during gestation, but additional deletion of p53 rescues them from death [47].

Since MDM2 and p53 form a regulatory feedback loop, any change in MDM2 expression would affect p53 expression and consequently play a critical role in cancer development. Much work has been done to uncover the mechanisms by which MDM2 is over-expressed in human cancers. One mechanism is through enhanced protein translation, which has been found in several cancer cell lines, including Burkitt's lymphoma cells [48], cutaneous melanoma cells [49], and breast cancer cells [50]. Interestingly, the translational regulation of MDM2 is linked to alternative promoter usage. The constitutive P1 promoter produces transcripts lacking exon 2 whereas the p53-responsive P2 promoter generates transcripts lacking exon 1 [51]. Consequently, mRNAs transcribed from the P1 promoter contains a long 5' UTR (L-MDM2) whereas mRNAs from the P2 promoter contains a short 5' UTR (S-MDM2). However, the polypeptides translated from these mRNAs are identical. Interestingly, the rate of ribosome loading to the long 5' UTR is slow and thus the level of the constitutively expressed MDM2 protein is low. In contrast, the short 5' UTR in S-MDM2 was found to enhance translation (Bortner and Rosenberg, 1997). Importantly, in some human breast cancer cells, S-MDM2 is predominantly produced, leading to an overabundance of MDM2 protein that represses p53 [50].

Several RBPs have been shown to regulate MDM2 expression. Trotta et al reported that RNA-binding protein La is required for enhanced MDM2 translation in a BCR/ABL-expressing myeloid precursor cell line [52]. The enhanced translation is through a direct binding of La to a 27-nt segment in the 5' UTR of S-MDM2 mRNA. Specifically, La over-expression led to increased MDM2 levels and enhanced resistance to apoptosis. In contrast, targeting endogenous La by La siRNAs or a dominant negative La mutant led to attenuated expression of MDM2 as well as enhanced susceptibility to DNA damage-induced apoptosis. We would like to mention that several ribosomal proteins, such as L5, L11, and L23, also regulate MDM2-p53 feedback loop by interacting with MDM2 and inhibiting its E3 ubiquitin ligase activity. But a detailed discussion of this regulation is beyond the scope of this review.

Recently, Met, the hepatocyte growth factor (HGF) receptor and IGF-1R, the insulin like growth factor 1 receptor, were found to regulate MDM2 translation [53,54]. By signaling through PI3K and mTOR, Met promoted MDM2 translation and subsequently degraded p53 and increased cell survival [53]. Since up-regulation of Met signaling in combination with down-regulation of p53 activity is often found in human liver carcinomas [55], this suggests that inhibition of p53 is one of the mechanisms by which Met promotes liver tumorigenesis. Similarly, IGF-1R was found to be required for MDM2 translation since inhibition of IGF-1R decreased MDM2 translation. Interestingly, p53 translation was also shown to be decreased upon IGF-1R inhibition [54]. Since MDM2 is a negative regulator of p53, inhibition of IGF-1R would have two opposing effects on p53 expression: decreased p53 translation and increased protein stability.

Regulation of p21

p21, a well-characterized p53 target, is a cyclin-dependent kinase inhibitor (CDK) and controls the cell cycle transition from G1 to S [56,57]. In addition to its transcriptional regulation by p53 or other transcriptional factors, p21 is also found to be regulated by posttranscriptional mechanisms, including mRNA stability and translation. For example, the stability of p21 transcript was found to be increased in cells irradiated with ultraviolet C (UVC) in a p53-dependent manner [58] and in cells treated with various agents, such as tumor necrosis factor α [59], epidermal growth factor (EGF) [60], prostaglandin A2 [61], and phorbol myristate acetate [62]. Furthermore, the 3' UTR of p21 mRNA, which contains several cis-acting elements, was found to be a target for several RNA-binding proteins. For instance, upon exposure to UVC or treatment with EGF and prostaglandin A2, HuR was translocated from nucleus to cytosol, where it bound to the 3' UTR in p21 transcript and enhanced its stability [60,63,64]. Like HuR, HuD, a neuronal member of the Elav-like family, was shown to bind to and stabilize p21 transcript [65]. Similarly, Poly(C)-binding protein (CP1) and NF90, a double strand RNA-binding protein, was found to stabilize p21 mRNA in MDA-468 cells and developing skeletal muscles, respectively [60,66]. Recently, we showed that RNPC1, an RNA-binding protein and a target of the p53 family, is required for maintaining the stability of the basal and stress-induced p21 transcript by binding to the 3' UTR of p21 mRNA [67].

The expression of p21 is also regulated by several RBPs through the translational mechanism. For instance, CUG-binding protein 1 (CUGBP1) and calreticulin (CRT) were found to differentially regulate p21 translation by binding to the same region in the 5' UTR of p21 mRNA. CRT inhibited p21 translation and abolished p21-dependent growth arrest and cellular senescence. Conversely, CUGBP1 blocked CRT-mediated inhibition of p21 translation and promoted p21-dependent growth arrest and cellular senescence [68]. Moreover, hnRNP K, a KH domain-containing RBP, was found to repress p21 translation by directly binding to the CU-rich elements in the 3' UTR of p21 mRNA and antagonizing the enhanced mRNA stability mediated by HuB [69]. Similarly, Musashi-1, another RRM-containing protein, was reported to repress p21 translation by directly binding to the 3' UTR of p21 mRNA [70].

Regulation of Gadd45 α

The growth arrest and DNA damage-inducible (GADD) 45 gene family consists of GADD45 α , GADD45 β , and GADD45 γ . Gadd45 α encodes a 21-KDa protein, whose level can be rapidly increased in cells exposed to a variety of agents, including DNA damaging agents, hypoxia, ionizing radiation, oxidants, ultraviolet light, and growth-factor withdrawal [71]. Gadd45 α is found to be involved in G2/M arrest, apoptosis, DNA repair, and genome stability [71-74].

Gadd45 α expression has been extensively studied. Numerous transcriptional factors have been identified to modulate Gadd45 α expression. p53, FoxO3a, and Egr-1 up-regulate Gadd45 α expression while c-myc and ZBRK repress Gadd45 α expression [75-79]. Interestingly, Gadd45 α expression is also regulated through posttranscriptional mechanisms, such as mRNA stability and translation. Gadd45 α mRNA was found to be stabilized upon treatment with MMS, UV, glutamine deprivation, retinoid CD437, and arsenic [80-83]. In addition, a 45-nt element in the 5' UTR of Gadd45 α mRNA is required for CD437-mediated Gadd45 α mRNA stability [83]. Moreover, arsenic was found to enhance Gadd45 α translation via an IRES element in the 5' UTR of Gadd45 α mRNA in growth-arrested cells [84]. Recently, Lal et al showed that AU-rich element RNA-binding factor 1 (AUF1) and T-cell-restricted intracellular antigen-1-related protein (TIAR) repress Gadd45 α expression by binding to the AU-rich element located at the 3' UTR of Gadd45 α mRNA. Specifically, in unstimulated cells, AUF1 and TIAR proteins were found prominently in a complex containing Gadd45 α mRNA. AUF1 markedly reduced Gadd45 α mRNA stability whereas TIAR potently inhibited Gadd45 α translation. In response to genotoxic stresses, AUF1 and TIAR were dissociated from the complex containing Gadd45 α mRNA, leading to enhanced stability and translation of Gadd45 α mRNA.

Conclusion and perspectives

The importance of gene regulation by posttranscriptional mechanisms, particularly at the level of mRNA decay and translation, is becoming apparent. Here, we have described the involvement of various RBPs in regulating the p53 pathway. It is clear that both p53 and its targets can be regulated by RBPs through mRNA stability and translation. Moreover, one given RBP can regulate multiple targets in the p53 pathway. For example, HuR regulates the expression of p53 and p21 via translation and mRNA stability [29,63], respectively. In addition, one given mRNA, such as p53 and MDM2, can be regulated by multiple RBPs. Although many RBPs and their RNA targets have been identified, the mechanisms still remain to be elucidated. First of all, how does a RBP choose to regulate its RNA targets? Is the RNA recognition sequence in the target the sole determinant or does a stress signal impact on its target selection? Secondly, how do multiple RBPs control the expression of one given transcript and how do they coordinate? Thirdly, although many p53 targets can be regulated by RBPs via p53, some p53 targets are directly regulated by RBPs independent of p53, such as MDM2, GADD45a, and p21. Thus, how do p53 and RBPs coordinate to regulate their common targets? Lastly, several RBPs, including MCG10 [85], Wig-1 [86], and RNPC1 [67], can be transactivated by p53. Interestingly, all these RBPs are capable of inhibiting cell proliferation. Therefore, do they play a unique role in growth inhibition mediated by the p53 pathway? And are there additional RBPs that can be regulated by p53?

Of particular interest, many cancers that retain the wild type p53 gene do not possess a functional p53 pathway. One proposed mechanism is that aberrant RBP expression plays a role in inactivating the p53 pathway. For instance, La-mediated translational control of MDM2 is functionally relevant to the pathogenesis of BCR/ABL leukemogenesis by promoting p53 degradation or inhibiting its transcriptional activity. In addition, thymidylate synthase has been

found to be over-expressed in several colon cancers [87]. Therefore, translational repression of p53 by thymidylate synthase may represent an efficient mechanism for cancer cells to escape cell cycle checkpoints and apoptosis. These findings highlight the [21] importance of RBPs in the p53 pathway, which may be used as targets for therapeutic intervention. For example, we may envision that by disrupting the interaction of La to the 5' UTR in MDM2 mRNA and subsequently inhibiting MDM2 expression, p53 activity would be increased to suppress cancer development.

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