The role of the 5′ terminal region of p53 mRNA in the p53 gene expression

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The p53 tumour suppressor protein is one of the major factors responsible for cell cycle regulation and protection against cancer development. This is why it is often referred to as “the guardian of the genome”. On the other hand, mutations in the p53 gene are connected with more than 50% of tumours of various types. The thirty-six years of extensive research on the p53 gene and its protein products have shown how sophisticated the p53-based cell system control is. An additional level of complexity of the p53 research is connected with at least twelve p53 isoforms which have been identified in the cell. Importantly, disturbance of the p53 isoforms’ expression seems to play a key role in tumorigenesis, cell differentiation and cell response to pathogenic bacteria, and RNA and DNA viruses. Expression of various p53 isoforms results from the usage of different transcription promoters, alternative splicing events and translation initiation from alternative AUG codons. The importance of the 5′-terminal regions of different p53 mRNA transcripts in the multi-level regulation of the p53 gene has recently been documented. In this review we focus on the structural features of these regions and their specific role in the p53 translation initiation process.

Key words: p53, transcription, translation, non-coding region, mRNA, IRES

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INTRODUCTION

The p53 protein was described in 1979 as a factor interacting with the T antigen of virus SV40 (Lane & Crawford, 1979; Linzer et al., 1979). Early on, p53 was thought to act as a proto-oncogene since many tumor tissues exhibit mutations in the p53 gene. This view has changed when analyses of specific mutations in the p53 gene in colorectal carcinoma suggested that due to these changes the p53 protein is dysfunctional, whereas the wild-type gene product might actually act as a tumor suppressor (Baker et al., 1989). Additionally, it has been demonstrated that overexpression of wild-type p53 causes suppression of carcinogenesis (Eliyahu et al., 1989; Finlay et al., 1989). Since then, there have been many discoveries regarding the p53 protein and its function in the cell. Nowadays, it is known that p53 is involved in the cell cycle control, apoptosis and it acts as a tumor suppressor (Marcel et al., 2011).

Under physiological conditions, p53 concentration in the cell is maintained at a low level due to interactions with the E3 ubiquitin-ligase Hdm2 (human homolog of mouse double minute 2) (Brooks & Gu, 2011; Wang & Li, 2010). Stress events cause phosphorylation of the p53 protein to prevent the p53-Hdm2 interaction and, as a consequence, the p53 level is elevated (Powell et al., 2008; Wang & Li, 2010). As a transcription factor, p53 activates many genes which are engaged in growth arrest, DNA repair and the restoration of cell homeostasis (Olivares-Illana & Fahrenqu, 2010). Mutations in the p53 gene lead to the loss of genome integrity and tumorigenesis (Muller & Vousden, 2013).

Over the last 25 years, the full-length p53 protein was believed to be the only product of p53 gene expression. In 2002, the discovery of the N-truncated form of p53 lacking 40 amino acids from the N-terminus, Δ40p53, marked the beginning of comprehensive systematic studies aimed to identify other isoforms of p53 and to understand their function in the cell (Courtois et al., 2002). Nowadays, at least 12 isoforms of the p53 protein are known whose expression results from the usage of various transcription promoters, alternative splicing and various translation initiation sites (Marcel & Hainaut, 2009; Khoury & Bourdon, 2010, 2011).

All these cellular events are strongly dependent on the sequence and structure of p53 mRNA, particularly on its non-coding regions. It has been noticed that the known p53 protein isoforms show tissue specificity and their expression levels vary depending on the tissue type (Takagi et al., 2005). It is extremely important that disturbance of the p53 isoforms’ expression seems to play a key role in tumorigenesis (Bourdon, 2007; Khoury & Bourdon, 2011; Marcel et al., 2011), cell differentiation (Ungewitter & Scramble, 2010), and cell response to pathogens: Helicobacter pylori (a Gram-negative bacterium), and RNA and DNA viruses (the influenza virus and SV40) (Terrier et al., 2013).

In this paper, functions of the 5′-terminal region of p53 mRNA in the p53 gene expression are reviewed. Particularly, we focus on the structural features of this region in different p53 transcripts and their specific role in the p53 translation initiation process.

HUMAN P53 MRNA TRANSCRIPTS AND P53 ISOFORMS

Transcription of the p53 gene is initiated from at least five sites: P0, P1, P1’, P2 and Pn (Fig. 1). Promoter regions P0, P1, P1’ are located in the first exon, whereas the other two promoters, P2 and Pn, are positioned in the introns. Promoter P0 is positioned near the 5′ end of the p53 gene and the corresponding p53 transcript contains...
the 5' untranslated region (5'UTR) of approximately 250 nucleotides in length (Lamb & Crawford, 1986). The P1 promoter region is located about 110 nucleotides downstream in the sequence of the gene. Transcription from the P1 start site can be heterogeneous, as several p53 mRNAs contain the 5'UTR consisting of approximately 140 nucleotides. Between the P0 and P1 regions, there is a P1' transcription initiation site which generates a 190 nucleotide-long 5'UTR (Tuck & Crawford, 1989; Strudwick et al., 2003). The P53 mRNA transcripts synthesized from P0, P1 and P1' promoters, are templates for the translation of full-length p53 initiating from the AUG1 codon, which is located at the beginning of exon 2. The shorter isoform of p53 protein, Δ40p53, which lacks the first 40 aminoacids, is translated from AUG2 present in exon 4 (Courtois et al., 2002). The Δ40p53 isoform may be synthesized as a result of retention of the entire intron 2 sequence (with three stop codons) in the p53 mRNA and translation re-initiation (Ghosh et al., 2004) or according to the mechanism of internal initiation with the use of the IRES element (Internal Ribosomal Entry Site) (Ghosh et al., 2004; Ray et al., 2006). The use of the P0 transcription start site, which is located in intron 1, results in mRNA whose function has not yet been identified (Reisman et al., 1988). The P2 transcription start site, located in intron 4, generates a transcript encoding two p53 isoforms: Δ133p53 (Bourdon et al., 2005) and Δ160p53 (Marcel et al., 2010). Additionally, variants of the p53 protein and its ΔN-truncated isoforms which differ at the C-terminus (α, β and γ variants), resulting from alternative splicing of intron 9, have been identified in the cell (Marcel et al., 2011).

The transcription pattern of the p53 gene remarkably differs between normal and tumor tissues. It has been observed that P0- and P1'-initiated transcripts appear in the normal tissue, whereas P1-initiated p53 mRNA predominates in tumorigenic or non-tumorigenic immortalized cell lines (Strudwick et al., 2003). Additionally, it has been observed that in a majority of the tested normal human tissues, 50% of the total p53 mRNAs is defined as a P0-initiated transcript. Nevertheless, in mammary glands, spleen and thymus all the three types of the p53 transcript appear which confirms the diversity in transcription of the p53 gene (Strudwick et al., 2003).

A structural analysis of the 5'-terminal region within a P1-initiated mRNA transcript has revealed the presence of a large G56–C169 thermodynamically stable hairpin and the second, smaller U180-A218 stem-loop (Błaszczyk & Ciesiołka, 2011). Additionally, it has been demonstrated that the coding sequence is necessary for proper folding of the 5' terminus of the P1-initiated transcript (Błaszczyk & Ciesiołka, 2011). In vitro and in vivo experiments have shown that the P0-P1 region influences p53 translation efficiency (Strudwick et al., 2003; Górka et al., 2013). Interestingly, it has been shown that two
characteristic hairpin elements, G56–C169 and U180-A218, are preserved in the P0-initiated transcript (Górska et al., 2013). In the P1-initiated mRNA both translation initiation codons, AUG1 and AUG2, are located in the helix-bulge junction and the A residues are unpaired. Moreover, the AUG1 triplet is embedded within the large G56–C169 hairpin and despite favorable Kozak context of this initiation codon, a low level of p53 synthesis is observed (Kozak, 1989). The structural environment of AUG1 is likely to limit the p53 translation efficiency (Blaszczyk & Ciesiolka, 2011; Kozak 2005). Structure probing of the 5′ terminus of the P1-initiated mRNA with intron 2 retained, has shown that the large hairpin containing the AUG1 codon is also preserved in this transcript (Górska et al., 2013). Thus, the presence of G56–C169 hairpin in which the AUG1 codon is embedded in various p53 mRNA transcripts strongly indicates an important role of this motif in the p53 gene expression. Moreover, it has been suggested that the structural neighborhood of AUG2 might also influence the synthesis of the Δ40p53 isoform. In the P1-initiated p53 mRNA, in the proximity of AUG2, a thermodynamically unstable hairpin has been detected, which consists mainly of AU and GU base pairs. This motif may participate in the regulation of the Δ40p53 translation via interaction with specific proteins (Blaszczyk & Ciesiolka, 2011).

In summary, variations of the p53 transcripts in normal and tumor cells, the observed impact of the P0–P1 region on the p53 protein synthesis and the specific structural context of initiation codons, indicate a coupled transcription/translation regulatory system which is based on structural elements present in the 5′-terminal region of p53 mRNAs (Bienz-Tadmor et al., 1985; Lamb & Crawford, 1986; Strudwick et al., 2003).

REGULATION OF THE P53 TRANSLATION INITIATION

Expression of the p53 gene is controlled not only at the transcriptional level but also at the translational level. Owing to the use of alternative initiation codons, more than one protein may be produced from the same mRNA transcript. The most abundant members of the p53 family include the full-length p53 protein which is generated from AUG1, and the Δ40p53 isoform which is generated from the AUG2 internal codon (Fig. 3). Translation of proteins with alternative initiation codons may take place by re-initiation, by leaky scanning by the ribosome or by the IRES: all these possibilities have been discussed with regard to the synthesis of Δ40p53 (Blaszczyk & Ciesiolka, 2011). Importantly, it has been demonstrated that the longer 5′ terminus of p53 mRNA strongly reduces the synthesis of the p53 and Δ40p53 proteins (Górska et al., 2013). This is consistent with the observations that the longer 5′UTR results in lower productivity of the cap-dependent translation system (Vasilienko et al., 2011).

It is postulated that several proteins which play a crucial role in the cell cycle regulation and apoptosis may be translated in a cap-independent manner. The p53 protein is an example of such a protein, since it is involved in the processes of cell cycle control and carcinogenesis (Stoneley & Willis, 2004; Sonnenberg & Hinnebusch, 2009). Early studies of the 5′ terminus of p53 mRNA with regard to the presence of the IRES element have begun with the observation that cells subjected to stress demonstrate different expression levels of the p53 and Δ40p53 proteins (Candeias et al., 2006). At the same time, the mRNA levels remain intact. Importantly, the Δ40p53 isoform does not contain the TADI domain, which mediates the Hdm2 binding and p53 ubiquitination. Therefore, the changes in Δ40p53 amounts are not due to protein degradation. Moreover, in vitro studies of the p53 and Δ40p53 translational inhibition in the presence of a free cap analog have revealed that protein synthesis initiating from AUG1 is strongly impaired, while translation from AUG2 is only slightly reduced. This indicates that translation from AUG2 for the Δ40p53 isoform is cap-independent (Górska et al., 2013). Additionally, the high GC content in the sequence of the 5′ terminus of p53 mRNA and the presence of thermodynamically stable hairpin structures support the hypoth-

Figure 3. Cap- and IRES-dependent translation initiation of full-length p53 and its Δ40p53 isoform.

In cap-mediated translation, 43S PIC (pre-initiation complex) scans the 5′-terminal region of p53 mRNA to find the first initiation codon for full-length p53. On the other hand, leaky scanning or reinitiation allow translation initiation from AUG2 for Δ40p53. IRES-driven translation of both proteins: p53 and Δ40p53, is based on recognition of the structural motifs within the 5′ terminus of p53 mRNA by the ribosomal initiation complex. This process is supported by auxiliary factors, ITAFs.
exist that this region may contain the IRES elements (Błaszczyk & Ciesiolk, 2011). It has been observed that IRES-mediated translation of the p53 protein is increased in response to cellular stress. It turns out that endoplasmic reticulum stress, glucose deprivation or IR radiation causing DNA damage may increase the p53 protein production by elevating the interaction of the p53 5'UTR with regulatory proteins (Candeias et al., 2006; Bourougaa et al., 2010; Khan et al., 2015). Bellodi and colleagues have demonstrated the important role of the p53 IRES in cancer susceptibility (Bellodi et al., 2010). They have associated the defective functioning of the IRES with impairments in oncogene-induced senescence and with an increased probability of cancer development in an X-linked genetic disorder, dyskeratosis congenita (Bellodi et al., 2010). Additionally, it has been shown that silent mutations introduced within the 5' terminus of p53 mRNA greatly reduce the IRES-driven translation in the cells (Grover et al., 2011). It appears that any defects in the structure and/or sequence of the IRES element lead to reduction of its activity and cause malfunctions in the cell and disease development (Sharathchandra et al., 2012). Probably, this is due to the disruption of the IRES structural integrity and the lack of interaction with ITAFs (IRES trans-acting factors) which are able to modulate the IRES activity. Moreover, changes in the folding of the IRES structure may affect the ribosome assembly on the mRNA (Grover et al., 2011). It has been demonstrated that treatment with antisense oligonucleotides which disturb the IRES structure, results in decrease in the translation efficiency of the Δ40p53 isoform under stress conditions (Swiatkowska et al., 2015). These studies have confirmed that proper folding of the 5' terminus of the p53 mRNA is essential for maintaining the IRES activity and the synthesis of the Δ40p53 isoform.

Interestingly, the translation of p53 and Δ40p53 proteins appears to be cell cycle-dependent and occurs most actively at certain phases of the cycle (Ray et al., 2006). During transition from the G1 phase to the synthesis phase, the translation mediated by the IRES element increases, which results in the production of the Δ40p53 protein. Subsequently, the Δ40p53 isoform interacts with the p53 protein and inhibits its activity, which enables the synthesis phase to begin. On the other hand, the p53 protein is produced during transition from the G2 stage to the mitosis phase, despite inhibition of the cap-dependent translation. However, the amount of p53 is maintained at a low level due to the interaction with Hdm2, which enables the start of mitosis (Ray et al., 2006; Bourougaa et al., 2010). Therefore, it seems that the proportion of p53 to Δ40p53 proteins and the differential activity of the IRES are among the essential factors in the cell cycle regulation.

PROTEINS AND NON-CODING RNAs INTERACTING WITH THE 5'-TERMINAL REGION OF P53 mRNA

Recent studies have shown that protein factors may play an important role in p53 expression acting as ITAFs to enhance the p53 IRES-mediated translation, particularly under stress conditions (Grover et al., 2008). These factors are able to recognize specific structural domains of the 5'-terminal region of p53 mRNA (Candeias et al., 2008; Grover et al., 2008; Khan et al., 2013). It seems that the presence of protein factors facilitates maintaining of the proper IRES structure and ribosome complex assembly. On the other hand, binding of specific proteins to the 5' end of p53 mRNA may result in a decrease in p53 translation efficiency in untreated cells (Wedeen et al., 2011). It has been also observed that p53 translation and p53 mRNA decay are modulated by a non-coding RNA which is able to associate with the p53 5'UTR (Farnebo 2009; Mahmoudi et al., 2009). In this section we present current knowledge on proteins and non-coding RNA molecules that are involved in p53 expression regulation via interactions with the 5' terminus of p53 mRNA (Table 1).

Hdm2 is one of the main regulators of the p53 protein level in the cell (Powell et al., 2008; Wang & Li, 2010). Under normal conditions, Hdm2 ubiquitinates the p53 protein which is subsequently degraded by proteasome. However, the Fahraeus' group has demonstrated that Hdm2 does not only interact with the p53 protein but it binds to p53 mRNA as well (Candeias et al., 2008). The small U180-A218 hairpin of the 5' terminus of p53 mRNA is likely to be the binding site of the Hdm2 protein. It has been observed that p53 translation is stimulated by the Hdm2–p53 mRNA interaction. Moreover, a synonymous L22L mutation (codon in position 22, CUA to CUG) located in the apical loop of the U180-A218 hairpin results in the reduction of the p53 and Δ40p53 translation level. The L22L mutation probably causes the alteration of the tertiary structure of the U180-A218 hairpin which reduces binding of the Hdm2 protein to this region (Candeias et al., 2008).

PTB1 (polypyrimidine tract binding protein 1) is another protein which has been shown to modulate the p53 translation efficiency via association with the 5' terminial region of p53 mRNA. (Sawicka et al., 2008). This factor is involved in many processes in the cell, such as alternative splicing, polyadenylation regulation and RNA transport (Sawicka et al., 2008; Schellenberg et al., 2008). Moreover, PTB1 may interact with viral IRES elements acting as an ITAF to stimulate the virus translation (Sawicka et al., 2008; Gallego, 2002). Recently, there is more and more evidence that PTB1 may also bind to cellular IRESes to enhance cap-independent translation when the classic translation pathway is impaired, mostly under stress conditions (Fitzgerald & Semler, 2009). Such regulation has been observed in the case of p53 translation (Grover et al., 2008; Khan et al., 2013). The PTB1 protein interacts with the coding region between AUG1 and AUG2, as well as with the 5'UTR of p53 mRNA (Grover et al., 2008). Upon stress conditions, PTB1 seems to enhance the p53 and Δ40p53 synthesis, acting as an ITAF. Recently, the role of PTB1 in p53 expression has been additionally supported by the observation of an impact of a single-nucleotide polymorphism in the 5' terminus of p53 mRNA on the p53 translation (Khan et al., 2013). Presence of polymorphism at position 119 (C to T) of the large hairpin reduces the IRES-dependent translation, probably due to a weaker interaction with the PTB1 protein. Additionally, a track of pyrimidines within the U180-A218 hairpin is another possible binding site for the PTB1 protein (Khan et al., 2013).

Annexin A2 and PSF (PTB associated splicing factor) have been also proposed as ITAFs for p53 IRES (Sharathchandra et al., 2012). Both proteins partly associate with the same regions of the 5' terminus of p53 mRNA, in close proximity to the initiation codons for p53 and Δ40p53, indicating their potential role in ribosome positioning. Stress conditions result in an increase in annexin A2 and PSF binding to the 5' end of p53 mRNA. Probably, their interactions stimulate the IRES activity since a higher translation level of p53...
and Δ40p53 is observed. PSF also associates with PTB which enhances the p53 IRES. Moreover, both PSF and PTB seem to bind to similar fragments of the 5′ terminus of p53 mRNA (Sharathchandra et al., 2012; Khan et al., 2013). However, silencing of both PSF and PTB affects the p53 level so that it is comparable to the one achieved by knocking down the PSF or PTB alone, which indicates a lack of a cumulative effect (Sharathchandra et al., 2012).

The U180-A218 stem-loop is postulated to interact not only with Hdm2 or PTB (Candeias et al., 2008; Grover et al., 2008; Khan et al., 2013), but also with hnRNP C1/C2 (heterogeneous nuclear ribonucleoprotein C1/C2) (Candeias et al., 2008; Christian et al., 2008). The hnRNP C1/C2 takes part in the pre-mRNA assembly, contributes to mRNA stability and presumably takes part in the translation initiation of cellular mRNAs which possess the IRES elements (Haley et al., 2009). It has been shown that hnRNP C1/C2 exhibits a strong affinity to the U180-A218 hairpin under stress conditions, which is accompanied by a higher efficiency of p53 translation (Candeias et al., 2008; Grover et al., 2011). Moreover, partial depletion of the hnRNP C1/C2 causes a decrease in the p53 and Δ40p53 synthesis indicating that hnRNP C1/C2 may act as a positive regulator of p53 expression at the translational level (Grover et al., 2011).

In UV-irradiated cells enhancement of p53 translation has been shown upon binding of ribosomal protein RPL26 to the 5′UTR of p53 mRNA (Takagi et al., 2005; Mahmoudi et al., 2009). The RPL26–p53 5′UTR interaction results in an increased association of p53 mRNA with polysomes. As a consequence, a higher translation level of p53 and, subsequently, induction of the G1 cell-cycle arrest have been observed. The highest p53 translation efficiency was observed when the 5′UTR contained only the first 75 nucleotides. The presence of a longer untranslated region caused a decrease in the p53 amount indicating a potentially negative structural regulator of the p53 synthesis in a further region of the 5′ non-coding part of p53 mRNA (Takagi et al., 2005). Additionally, RPL26 may bind to a double-stranded region resulting from long-range interactions between the 3′ and 5′ ends of p53 mRNA (Chen & Kastan, 2010). It has been also proposed that during stress events, a similar fragment of the 5′UTR may be recognized by nucleolin, which is involved in ribosome synthesis and maturation (Takagi et al., 2005; Mahmoudi et al., 2009). However, overexpression of nucleolin diminishes p53 translation which means that both proteins, RPL26 and nucleolin, might compete for the same binding site along the 5′ non-coding region of p53 mRNA (Takagi et al., 2005).

The p53 suppression is caused by Pdcd4 protein (programmed cell death protein 4), which controls the expression of many genes by inactivating specific transcription factors (Lankat-Buttgereit & Goke, 2009). It has been demonstrated that Pdcd4 is able to interact with the 5′UTR of p53 mRNA under physiological conditions to facilitate maintenance of a low level of the p53 protein in the cell (Wedeken et al., 2011). Binding of Pdcd4 to the 5′non-coding fragment of p53 mRNA mediates the formation of the Pdcd4-eIF4A complex which blocks the helicase activity of eIF4A (Wedeken et al., 2011). A weaker activity of eIF4A results in the inhibition of p53 translation. Since the Pdcd4 expression is reduced in the presence of a DNA-damaging agent, it seems to be one of the factors engaged in the control of the p53 expression in untreated cells.

The 5′ untranslated region of p53 mRNA is also a potential binding site for various non-coding RNAs which are able to modulate its expression. However, only one long non-coding RNA, Wrap53, has been identified so far, which may control the p53 mRNA expression by association with its 5′UTR (Mahmoudi et al., 2009). Exon

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1 of Wrap53 RNA binds to exon 1 of p53 mRNA, with full complementarity between nucleotide positions 44 and 157 (Mahmoudi et al., 2009). Despite the low level of Wrap53 in the cell, it may efficiently modulate the p53 RNA and protein level (Farnebo 2009; Mahmoudi et al., 2009). Since silencing of Wrap53 expression causes a decrease in the p53 mRNA and protein amount, this means that Wrap53 is a positive in trans acting regulator (Mahmoudi et al., 2009). Moreover, it has been shown that Wrap53 prevents p53 mRNA degradation, presumably by blocking specific regulatory sequences (Farnebo 2009).

In particular, it has been demonstrated that the 5'-terminal region of p53 mRNA plays a role of a docking platform for several protein and RNA factors which are able to modulate the p53 expression (Table 1). However, precise mechanisms of many of those protein-RNA and RNA-RNA interactions are yet not clear and further research is necessary.

CONCLUSIONS

Recent studies have greatly expanded our knowledge about p53 protein and its function in the cell. It has been shown that during the p53 gene expression several transcription promoters are used, the transcript undergoes alternative splicing and uses alternative translation initiation sites to generate multiple protein isoforms. However, the mechanisms which modulate the level of p53 protein in the cell upon different conditions are not fully understood and many questions remain to be answered. Most recently, a crucial role of the 5'-terminal regions of various p53 mRNA transcripts in the transcription/translation regulation has been documented. This shows new directions for research aimed at better understanding of the overall control system of the p53 gene expression under physiological and stress conditions.

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