

Delta133p53 Isoforms of Human TP53

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The *TP53* gene is a critical tumor suppressor and key determinant of cell fate which regulates numerous cellular functions including DNA repair, cell cycle arrest, cellular senescence, apoptosis, autophagy and metabolism. The delta133p53 isoforms are critical regulators of these biological processes in human physiology and diseases such as cancer.

Keywords: p53 isoforms ; $\Delta 133p53$

1. Introduction

TP53 gene is known as “the guardian of the genome” [1] highlighting its crucial role in maintaining genetic stability and preventing cancer formation. p53 is both a central sensor and a master regulator of cellular stresses. Its activation is adapted to the cell type and signal and induces a myriad of cellular responses such as DNA repair, cell cycle arrest, cellular senescence, apoptosis, autophagy and metabolism [2][3]. It is now known that wild-type *TP53* encodes, in tissue- and cell type-dependent manners, at least 12 different p53 protein isoforms: p53 α (canonical p53), p53 β , p53 γ , $\Delta 40p53\alpha$, $\Delta 40p53\beta$, $\Delta 40p53\gamma$, $\Delta 133p53\alpha$, $\Delta 133p53\beta$, $\Delta 133p53\gamma$, $\Delta 160p53\alpha$, $\Delta 160p53\beta$ and $\Delta 160p53\gamma$ [4].

The p53 family members interact with each other and can modulate each other's expression and biological activities. This includes the p63 and p73 family proteins which can also interact to regulate several common target genes. For example, in the absence of p63 and p73 binding to p53-responsive promoters, p53 fails to induce apoptosis in response to DNA damage demonstrating the significance of p53 family member interactions in p53 pathway activity [5].

2. Regulatory Mechanisms of the $\Delta 133p53$ Isoforms

2.1. RNA Level

The mRNAs encoding the $\Delta 133p53$ isoforms are produced from the internal *TP53* promoter in the intron 4. Each of the $\Delta 133p53$ isoforms is translated from the methionine codon 133 and produced through alternative splicing of mRNA from exon-9 to either exon-10 ($\Delta 133p53\alpha$), exon-9 β ($\Delta 133p53\beta$) or exon-9 γ ($\Delta 133p53\gamma$). This results in either the inclusion of the oligomerization and α C-terminal domains (62 amino-acids identical to those of canonical full-length p53 α), the β C-terminal domain (10 amino acids), or the γ C-terminal domain (15 amino acids), respectively (Figure 1). In addition, mRNAs encoding the $\Delta 133p53$ isoforms can also be translated from the methionine codon 160, which produces each of the $\Delta 160p53$ isoforms with the same C-terminal variations.

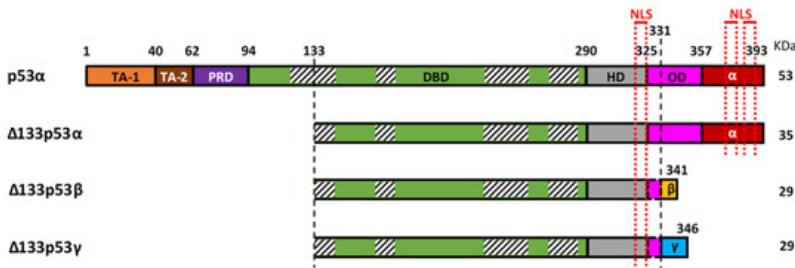


Figure 1. Representation of canonical p53 (p53 α) and the three $\Delta 133p53$ isoforms ($\Delta 133p53\alpha$, $\Delta 133p53\beta$ and $\Delta 133p53\gamma$). p53 α contains two transactivation domains (TAD1 and TAD2), the proline-rich domain (PRD), the DNA binding domain (DBD), the hinge domain (HD), the oligomerization domain (OD) and the α -domain. Part of the OD and the α -domain can be alternatively spliced to create the β and γ isoforms. The $\Delta 133p53$ isoforms lack TA-1, TA-2, PRD and part of the DBD. The DBD contains 4 highly conserved regions (striped boxes) spanning amino-acids 117–142, 171–181, 234–258 and 270–286 respectively, and the $\Delta 133p53$ isoforms lack, therefore, the majority of the first conserved region. Three nuclear localization sequences (NLS) are in the C-terminal part (red dotted lines), one in the HD and two in the α -domain, so the β and γ isoforms only have the first one.

The p53 isoforms are expressed in normal human tissues and are modulated by multiple mechanisms. Firstly, epigenetic events regulating the activity of the p53 proximal and internal promoters result in differential expression of $\Delta 133/\Delta 160$ α , β or γ mRNAs in normal human tissues [6]. In addition, the internal *TP53* promoter activity is influenced by polymorphisms, including the common pin3 (16-bp insertion in the intron-3) and R72P polymorphisms [7][8][9]. Furthermore, the internal promoter is transactivated by p53 α and several p63/p73 family members and is repressed by p68, a co-activator of p53-dependent transcription, particularly following genotoxic stress [8][10][11]. Finally, splicing factors, such as SRSF1 and SRSF3, regulate the alternative splicing of *TP53* intron-9 by inhibiting retention of exon-9 β/γ [12][13]. This results in reduced production of the β and γ isoforms. Consistent with this function, treatment with TG003, a small drug inhibitor of the Cdc2-like kinases (Clk), prevents Clk-induced activation of SRSF1 and SRSF3 leading to increased exon-9 β/γ inclusion [13]. In contrast to SRSF1 and SRSF3, SRSF7 has been reported to enhance β splicing in response to ionizing radiation (IR) [14]. In this context, IR reduces SMG1 (a PI3K-like protein) binding on p53 pre-mRNA which enables the recruitment of RPL26. This allows recruitment of SRSF7 which favors the inclusion of exon 9 β . Although these splicing factors primarily regulate the production of β/γ isoforms, SRSF1 has also been demonstrated to upregulate $\Delta 133$ p53 α expression without modulating canonical p53 α [15], suggesting a possible link between the regulation of alternative transcription and the alternative splicing. However, the exact mechanism of this regulation is not known.

2.2. Protein Level

At the protein level, the differential inclusion of canonical p53 domains in each of the p53 isoforms affects their behavior. The $\Delta 133$ p53 isoforms lack the first 132 amino-acids and are, therefore, devoid of the two transactivation domains (TADs) and part of the DNA-binding domain (DBD) (Figure 1). The DBD contains four conserved regions, the first of which spans between amino-acids 117 and 142, so the $\Delta 133$ p53 isoforms lack most of this first region but retain the three others. These four conserved regions coordinate Zn²⁺ loops structures which are essential for p53 conformation [16][17]. This suggests that the $\Delta 133$ p53 isoforms may have a different conformation as compared to their full-length counterpart. Although their conformation is not yet known, a recent study of the thermodynamic stability of $\Delta 133$ p53 β demonstrated that it has a higher aggregation propensity but can form a relatively stable complex with p53-specific DNA [18]. This suggests that there may be some differences in $\Delta 133$ p53 β conformation promoting aggregation but not enough to inhibit its binding to p53 response elements. The C-terminal region contains the hinge domain (HD), the oligomerization domain (OD), and the α regulatory domain (Figure 1). In the β and γ isoforms, part of the OD and the α domain are replaced by the β or γ domains, respectively. The lack of the OD in the β and γ isoforms may impair their ability to oligomerize with other isoforms. However, p53 β and p53 γ can still form DNA-mediated complexes with p53 α in the presence of p53-responsive promoter suggesting that the ability of these isoforms to interact with p53 α is not completely abolished [13]. In addition, the differences between the α , β or γ domains may impact cellular localization of the isoforms. In p53 α , there are three nuclear localization sequences (NLS): one in the HD and two in the α -domain (Figure 1). The $\Delta 133$ p53 α protein, which also contains all three NLS, is primarily located in the nucleus [6]. Although the $\Delta 133$ p53 β lacks two of the three NLS, it contains the HD-associated NLS and is detected in the cytoplasm and in the nucleus where it forms speckles. Interestingly, $\Delta 133$ p53 γ has the same NLS as $\Delta 133$ p53 β ; however, it is mostly detected in the cytoplasm. This indicates that β and γ domains are not equivalent and may suggest that either the β peptide modifies the subcellular localization or that the γ peptide counteracts the NLS activity.

Although MDM-2 binds to p53 mainly in the N-terminal TAD, it also contains a secondary binding site in the DBD which is common to all isoforms [19]. Camus et al. confirmed that MDM-2 binds to all p53 isoforms, including the $\Delta 133$ p53, without promoting their degradation [20]. Furthermore, they reported that all p53 isoforms are ubiquitinated and degraded by the proteasome with different kinetics in a cancer cell line. Hence, $\Delta 133$ p53 γ has the shortest half-life of all the isoforms, about 40 min, while $\Delta 133$ p53 α and $\Delta 133$ p53 β have half-lives of 110 and 135 min, respectively. The half-lives of all three $\Delta 133$ p53 isoforms were increased upon inhibition of the proteasome by MG-132 treatment, although the increase was smaller for $\Delta 133$ p53 β . It is, therefore, expected that MDM-2 can also block the transcriptional activities of most isoforms either directly or by recruiting corepressors such as hCtBP2 [21][22]. In addition to proteasome degradation, $\Delta 133$ p53 α is primarily degraded by chaperone-mediated autophagy during replicative senescence in normal human cells including fibroblasts, astrocytes and T-cells [23][24][25]. This process may be inhibited by direct interaction of the E3 ubiquitin ligase STUB1/CHIP with $\Delta 133$ p53 α or by pharmacological inhibition of autophagy by bafilomycin A1 [23].

Finally, one of the major regulatory systems of p53 stability and activity is post-translational modifications (PTM). The PTMs occurring on p53 α and their implications for its stability and activity have been extensively studied and described [26][27][28]. However, it is not known whether the same modifications occur on $\Delta 133$ p53 isoforms and, if so, whether they have similar effects. Given that the $\Delta 133$ p53 isoforms retain several of the PTM sites described in p53 α , and since the β (DQTSFQKENC) and γ (MLLDLRWCYFLINSS) C-terminal sequences also contain several serines, threonines, lysines or arginines residues, it is expected that several PTM can occur on all isoforms. In support of this expectation, p53 β and

p53 γ appear as several dots with different isoelectric points when visualized on 2D gels, suggesting different charges due to post-translational modifications [29][30][31][32]. In addition, as mentioned earlier, Camus et al. have reported that all p53 isoforms are ubiquitinated without necessarily promoting their degradation [20]. This suggests that ubiquitination of p53 isoforms may also be associated with proteasome-independent functions, including the regulation of subcellular location and protein interaction [33][34], further underscoring the potential for PTMs to modulate the stability and activity of p53 isoforms.

3. The Δ 133p53 Isoforms in Cancers

Clinical sample studies widely rely on qRT-PCR methods to determine the expression of mRNAs. Therefore, it is important to consider the technical limitations of the current detection methods. The first limitation is the difficulty to detect p53 isoforms expressed at lower abundance in patient samples or in RNA-seq databases [35]. Secondly, to specifically detect and quantify each of Δ 133p53 α , Δ 133p53 β and Δ 133p53 γ mRNAs separately, a simultaneous discrimination of N-terminal events (i.e., the transcriptional initiation for Δ 133p53/ Δ 160p53 versus that for p53 α and Δ 40p53) and C-terminal events (i.e., α , β or γ splicing) is required. Since Δ 133p53 α , Δ 133p53 β and Δ 133p53 γ mRNAs share a common region spanning 618 base-pairs, such simultaneous discrimination by qRT-PCR would need to amplify long amplicons, which may be difficult to obtain with conventional PCR methods and clinical RNA samples that could be partially degraded. Therefore, earlier clinical studies have only quantitated total expression levels of all three Δ 133p53 mRNAs without distinguishing between α , β or γ transcripts (Table 1, upper). Recent technical developments, such as RNAscope (RNA in situ hybridization), chromatography-tandem mass spectrometry and multiplex long amplicon droplet digital PCR, are beginning to circumvent these limitations [36][37][38] (Table 1, lower).

Table 1. Expression of Δ 133p53 isoforms in human cancer associated with disease progression, therapy response and patient prognosis.

Cancer Type	Total Δ 133p53 mRNAs (α , β and γ) Association with Disease
Colon cancer	Total Δ 133p53 mRNAs are downregulated in adenoma vs. normal tissue, but overexpressed in carcinoma vs. adenoma or normal tissue Total Δ 133p53 mRNAs expression is correlated with higher risks of recurrence Elevation of total Δ 133p53 mRNAs is associated with shorter disease-free survival
Cholangiocarcinoma	Total Δ 133p53 mRNAs upregulation, and decreased TA mRNAs, is associated with shortened overall survival Total Δ 133p53 mRNAs reduction sensitizes to 5-Fluorouracil treatment
Lung carcinoma	Total Δ 133p53 mRNAs are overexpressed in tumor as compared to adjacent non-cancerous tissue
Esophageal Squamous Cell Carcinoma	High tissue or serum total Δ 133p53/TAp53 ratio is associated with poor overall and progression-free survival.
Ovarian cancer	Total Δ 133p53 mRNAs expression in mutant <i>TP53</i> patients is associated with longer overall survival and disease-free survival Total Δ 133p53 mRNAs are associated with increased overall survival (and borderline disease-free survival) independently of <i>TP53</i> mutation status
Renal cell carcinoma	Wild-type tumors correlate with worse overall survival. Total Δ 133p53 mRNAs are downregulated in WT tumors compared to mutant tumors and normal adjacent tissue
Cancer Type	Single Specific Δ 133p53 Isoform Association with Disease
Breast cancer	Δ 133p53 α mRNA is detected in tumor but not in normal tissue Δ 133p53 β mRNA detection is associated with worse overall and disease-free survival Δ 133p53 β protein is overexpressed in invasive tumor as compared to non-invasive ones
Glioblastoma	Δ 133p53 β is elevated in glioblastoma malignant cells and is associated with immunosuppressive and chemoresistant environment
Prostate cancer	Δ 133p53 β mRNA is elevated in tumor vs. non-neoplastic tissue and is associated with shorter progression-free survival
Melanoma	Increased Δ 133p53 β mRNA expression is associated with poorer overall survival

The first part of the table displays the studies in which all three $\Delta 133p53$ mRNAs have been quantified as a whole, while the second part of the table displays the studies in which a single specific isoform has been identified.

Given their potency to regulate crucial aspects of the p53 response, investigation of associations between the $\Delta 133p53$ isoforms and cancer patient prognosis started shortly after their identification ([Table 1](#)). In colorectal cancers, total $\Delta 133p53$ mRNAs are downregulated in colon adenomas compared to non-tumor cells, but their expression is upregulated during the progression from adenoma to carcinoma ^[39]. This suggests that the total $\Delta 133p53$ isoforms may not promote benign tumor formation but may play a role in progression from benign to malignant tumors. Consistently, increased expression of total $\Delta 133p53$ mRNAs is associated with shorter disease-free survival and correlate with higher risks of recurrence ^{[40][41]}. This could be due to $\Delta 133p53\alpha$ -mediated activation of JAK-STAT3 and RhoA-ROCK signaling promoting colorectal cancer cell growth and invasion ^[41]. In addition, $\Delta 133p53\beta$ protein binds to and inhibits RhoB, thus preventing RhoB-induced apoptosis ^[40]. This may have important implications in tumor response to therapies such as camptothecin ^[40]. This is further supported by data from analysis of cholangiocarcinomas in which shortened overall patient survival is correlated with upregulation of total $\Delta 133p53$ mRNAs and downregulation of full length p53 mRNAs ($p53\alpha/p53\beta/p53\gamma$) ^[42]. Interestingly, targeting the $\Delta 133p53$ isoforms restores sensitivity to 5-Fluorouracil in resistant cholangiocarcinomas ^[43]. A possible explanation for this is the ability of $\Delta 133p53\alpha$ to enhance DNA repair ^{[52][53][54]}, which counteracts the effect of 5-FU. Critically, $\Delta 133p53\alpha$ may have a similar impact on other DNA-damage inducing cancer therapies. Similar upregulation of total $\Delta 133p53$ mRNAs has been observed in B-cell precursor acute lymphoblastic leukemia ^[55] and in lung carcinomas as compared to adjacent non-cancerous tissue ^[44] and is reported to increase cancer cell survival in pathogen-driven cancers such as gastric tumors associated with *H. pylori* ^[56]. In the case of gastric cancer, total $\Delta 133p53$ mRNAs expression correlates with the NF- κ B p65 subunit expression and may promote gastric cell growth ^[57]. Recently, a high total $\Delta 133p53$ /TAp53 ratio was shown to be a marker of poor overall and progression-free survival in esophageal squamous cell carcinoma ^[45]. Furthermore, specific changes in this ratio were correlated to clinical events. For example, the ratio quickly diminished following surgical resection of the tumor and increased upon tumor recurrence. Interestingly, this ratio was measured as circulating RNAs in patient's serum, which would represent a non-invasive, real-time method to monitor patient's recurrence.

Importantly, total $\Delta 133p53$ mRNAs expression is not always a bad prognostic marker. In mutant *TP53* serous ovarian cancer, patients expressing total $\Delta 133p53$ mRNAs have longer overall survival and disease-free survival ^{[46][58]}. Interestingly, a recent study on high-grade serous ovarian cancer established that high expression of total $\Delta 133p53$ mRNAs is correlated with increased overall survival independently of *TP53* mutation status ^[47]. This suggests that the association between total $\Delta 133p53$ mRNAs expression and good prognosis in serous ovarian cancers does not depend exclusively on *TP53* mutation status. This theory is reinforced by another recent publication which reported that wild-type (WT) *TP53* renal cell carcinomas (RCC) have a worse overall survival than those that harbor p53 mutations ^[48]. Interestingly, total $\Delta 133p53$ mRNAs were found downregulated in WT tumors as compared to non-tumor adjacent tissue, while they were unaffected in mutant tumors. This suggests that the worse prognosis in WT RCC may be due to the reduction of WT $\Delta 133p53$ expression.

In all the above studies, the clinical associations have been made with the expression level of all $\Delta 133p53$ mRNAs. Therefore, these associations cannot be linked to a biological activity of a specific isoform without cell-based functional assays (described below). Nevertheless, some studies using recent techniques of RNA quantification gathered insights into a possible role of individual $\Delta 133p53$ isoforms ([Table 1](#), lower). For example, using nested-PCR, $\Delta 133p53\alpha$ mRNA is detected in breast cancer samples but not in normal breast tissue ^[6]. However, it has also been shown that $\Delta 133p53\alpha$ is neither oncogenic nor mutagenic in normal human cells ([Table 2](#)) ^[54], which indicates that it may be involved in cancer progression once developed, but not in cancer formation. In breast cancer patients, detection of $\Delta 133p53\beta$ mRNA by nested-PCR is associated with worse overall and disease-free survival ^[49]. This was explained by its propensity to promote cancer invasion by triggering epithelial to mesenchymal transition ^{[49][50]}. Using the new RNAscope in situ hybridization and chromatography-tandem mass spectrometry techniques, increased $\Delta 133p53\beta$ expression was found to stimulate glioblastoma and prostate cancer development and aggressiveness by promoting an immunosuppressive and chemo-resistant microenvironment ^{[36][37]}. In prostate cancer, increased $\Delta 133p53\beta$ mRNA expression is associated with shorter progression-free survival ^[37]. Its increased expression has also been associated with poorer overall survival in melanoma ^[51].

Table 2. $\Delta 133p53\alpha$ is non-mutagenic and non-oncogenic in normal human cells.

Δ133p53α is	Because Δ133p53α
Non-mutagenic	Enhances DNA double-strand break repair
	Does not induce chromosomal and microsatellite repeats abnormalities
	Does not cause increased mutation rate, unlike canonical p53α knockdown
Non-oncogenic	Does not prevent p53α-dependent apoptosis of severely damaged cells
	Increases replicative lifespan without immortalizing cells
	Does not induce malignant transformation

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