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p53: Point Mutations, SNPs and Cancer

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1. Introduction

p53 was discovered in 1979 in SV40-transformed cells as a cellular protein that forms a complex with the large T antigen (DeLeo et al., 1979; Kress et al., 1979; Lane and Crawford, 1979; Linzer and Levine, 1979). It was originally identified as an oncoprotein, but was shown to be a tumor suppressor ten years later by both *in vitro* experiments and human tumor sample studies (Baker et al., 1989; Finlay et al., 1989; Hinds et al., 1989; Nigro et al., 1989).

Since then, an impressive body of work has been performed to decipher the functions and regulation of p53. The crucial role of p53 in tumor suppression is demonstrated by the fact that the *TP53* gene is mutated in 50-70% of human sporadic cancers (Levine, 1997), and that genes encoding the p53 regulators Mouse Double Minute 2 (Mdm2) and Mdm4 (also known as MdmX) are often mutated in the other tumors (Toledo and Wahl, 2006). Furthermore, germline *TP53* mutations account for the Li-Fraumeni syndrome, a familial cancer predisposition syndrome characterized by a high tumor penetrance and early tumor onset (Malkin et al., 1990).

More than 27 000 somatic mutations and close to 600 germline mutations of *TP53* were reported (according to the *TP53* mutation database (Petitjean et al., 2007) of the International Agency for Research on Cancer (IARC) ; release R15, November 2010). In this review, we summarize what *TP53* point mutations may reveal about p53 function and cancer development, and further address the prognostic and predictive values of *TP53* point mutations or SNPs in the p53 pathway.

2. Effects of point mutations in p53: Data from tumors and mouse models

In response to diverse oncogenic stresses, the transcription factor p53 promotes transient or permanent cell cycle arrest (the latter also known as senescence), or apoptosis, hence preventing cells with a damaged genome to proliferate (Vogelstein et al., 2000). In addition, p53 regulates various processes that may contribute to its tumor suppressive functions, including glycolysis, autophagy, cell mobility, microRNA processing, ageing and suntanning (Aylon and Oren, 2010; Cui et al., 2007; Vousden and Ryan, 2009).

Due to its detrimental activities to cell proliferation, p53 needs to be tightly regulated. Mdm2 and Mdm4 are the main p53 inhibitors (Wade et al., 2010), and their essential role is demonstrated by the p53-dependent lethality of Mdm2-deficient and Mdm4-deficient mouse embryos, which die from apoptosis or proliferation arrest, respectively. Mdm2 is a E3

ubiquitin ligase that can lead to the degradation of p53 by the proteasome (Brooks and Gu, 2006), whereas Mdm4 inhibits the activity of p53 mainly by occluding the p53 transactivation domain (Marine et al., 2006). But the regulation of p53 is much more complex, as more than 160 proteins interact with p53 to regulate its activity and stability (Toledo and Wahl, 2006).

The transcription factor p53 is a 393-amino acids protein composed of 5 domains : a N-terminal transactivation domain (TAD), a proline-rich domain (PRD), a core DNA binding domain (DBD), a tetramerization domain (4D) and a C-terminal regulatory domain (CTD) (Fig. 1A). Single-base substitutions in the *TP53* coding sequence, leading to missense mutations, nonsense mutations or frameshifts, are the principal mode of p53 alteration in human cancers (Olivier et al., 2010).

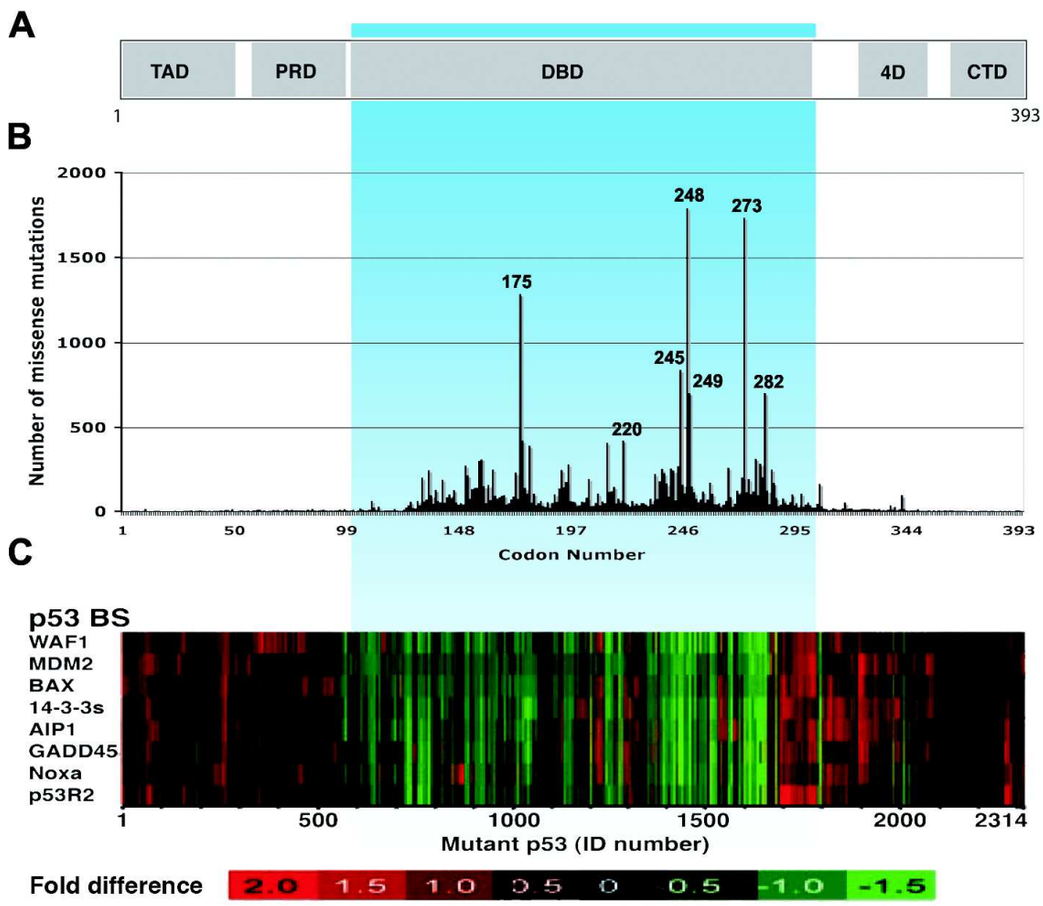


Fig. 1. *TP53* missense mutations are clustered in the DNA binding domain. (**A**) Schematic representation of the 5 domains of p53. (**B**) The number of missense somatic mutations in human cancers for each codon, according to the *IARC TP53* mutation database R15, was plotted against the p53 map. Data are from 20256 tumor missense mutations. The 7 most frequently mutated residues are indicated. (**C**) The transactivation activity of 2314 missense mutants tested in yeast and plotted against the p53 codon map. The capacity of mutants to transactivate 8 target genes (p21/WAF1, Mdm2, Bax, 14-3-3σ, AIP1, GADD45, Noxa and p53R2) relative to that of wild-type p53 is presented. (Modified from Toledo and Wahl, 2006).

2.1 *TP53* mutations in human cancers cluster in the DNA-binding domain

The functional importance of the p53 DNA-binding domain (DBD) is demonstrated by the fact that more than 70% of *TP53* mutations are missense mutations affecting residues within this domain (Fig. 1B), and leading to a decreased capacity in target gene transactivation (Fig. 1C).

Crystallographic studies showed that the p53 DBD consists of a central β-sandwich that serves as a scaffold for the DNA binding surface, composed of 2 structural motifs. The first loop-sheet-helix motif including loop L1 binds to the DNA major groove. The other half of the DNA binding surface contains two large loops L2 and L3, which interact with the DNA minor groove and can be stabilized by a zinc ion (Fig. 2). Compared to its paralogs p63 and p73, the p53 DBD has evolved to be more dynamic and unstable, with a melting temperature around 44-45°C (Joerger et al., 2006; Joerger and Fersht, 2008). Among the 7 residues most frequently mutated in human cancers, 6 are located at or close to the DNA binding surface (Fig. 2). Depending on their nature, these hotspot mutants can be classified as « contact » or « structural » mutants (Cho et al., 1994).

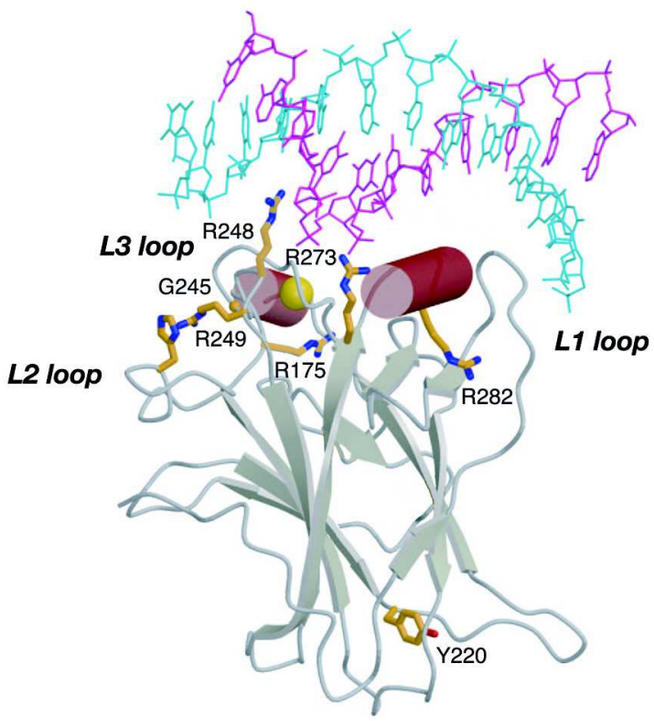


Fig. 2. Structure of the p53 DNA binding domain bound to DNA. The two strands of bound consensus DNA are shown in blue and magenta. The bound Zinc ion is shown as a golden sphere, and the 7 residues that are frequently mutated in human cancers are highlighted in orange (Modified from Joerger et al., 2006).

2.1.1 Contact mutants

Contact mutants affect the residues that interact directly with the DNA helix : residues R248 and R273 (Fig. 2). Crystallographic studies showed that R248 interacts with the minor groove of target DNA, whereas R273 contacts with the phosphate backbone at the center of

a p53 binding half-site (a p53 response element is composed of 2 binding half-sites separated by 0-13 base pairs, each half site corresponding to the consensus sequence 5'-RRRCWWGYYY-3', with R = G/A ; W = A/T and Y = C/T). This group of mutants encompasses hotspot mutations R248Q, R248W, R273H and R273C. Two of these were thoroughly studied in mouse models, in which each mutation was targeted at the p53 locus by using homologous recombination in embryonic stem cells.

The mouse model $p53^{R270H}$ (equivalent to human $p53^{R273H}$) revealed the dual property of the mutant protein (Olive et al., 2004). The $p53^{R270H}$ protein could exert dominant negative effects on the wild-type protein by hetero-oligomerization. Compared to their $p53^{+/-}$ counterparts, $p53^{R270H/+}$ mouse embryonic fibroblasts (MEFs) exhibited a faster cycling rate, and $p53^{R270H/+}$ thymocytes exhibited a decreased apoptotic response to γ-irradiation. Furthermore, $p53^{R270H/+}$ mice showed an increased incidence of spontaneous B-cell lymphomas and carcinomas with frequent metastases, a tumor spectrum distinct from that observed in $p53^{+/-}$ mice. In addition, mutant $p53^{R270H}$ exhibited gain-of-function phenotypes, as evidenced by the observation of a much higher incidence of various tumor types in $p53^{R270H/-}$ mice, including high-grade carcinomas with epithelial origin and hemangiosarcomas, which are rarely found in $p53^{-/-}$ mice. The authors attributed this gain-of-function effects to the inhibition of p63 and p73 functions by the mutant p53 protein.

In another study, the two most common p53 cancer mutations, R248W and R273H, were evaluated in mice after their independent targeting at the humanized *p53* knock-in ($p53^{hupki}$) allele. This humanized allele encodes a human/mouse chimeric protein containing human p53 residues 33-332 flanked by murine N-terminal and C-terminal p53 sequences (Song et al., 2007). Both mutants had lost p53-dependent cell-cycle arrest and apoptotic responses, and each showed a more complex tumor spectrum than $p53^{-/-}$ mice, suggesting a gain-of-function. Indeed, by interacting with the Mre11 nuclease and preventing the binding of the Mre11-Rad50-NBS1 complex to DNA double-strand breaks, the mutant proteins were found to disrupt a critical DNA-damage response pathway, and thus to promote genetic instability.

2.1.2 Structural mutants

The mutations of residues that are not in direct contact with DNA but function to stabilize the DNA binding structure are referred to as structural mutants. In contrast to contact mutants, structural mutants affect the overall architecture of the DNA-binding surface and change the conformation of the protein (Cho et al., 1994). Human cancer hotspot mutations R175H, Y220C, G245S, R249S and R282W belong to this category.

The residue R175 is the third most frequently mutated p53 codon in human cancers (Fig. 1B). Two different mutations affecting this residue were analyzed *in vivo*. Mouse models expressing a $p53^{R172H}$ protein (corresponding to $p53^{R175H}$ in humans) were found to be extremely tumor-prone. $p53^{R172H}$ led to the loss of both cell cycle control and apoptosis. In addition, a dominant-negative function of the mutant protein over wild-type p53 and the acquisition of an oncogenic function through p63 and p73 inactivation were reported (Lang et al., 2004; Olive et al., 2004). Another mouse model affecting the same residue is $p53^{R172P}$. This mutant was found unable to induce apoptosis, although it retained partial cell cycle control. Compared to $p53^{-/-}$ mice, $p53^{R172P/R172P}$ mice exhibited a delayed tumor onset ; this

indicated that apoptosis is not the only p53-dependent cellular response essential for tumour suppression, and that the maintenance of chromosomal stability is also important (Liu et al., 2004). More recently, further analyses of this mutant, in combination with a deficiency in Mdm2, revealed the importance of p53 and reactive oxygen species (ROS) in the regulation of pools of hematopoietic stem cells (Abbas et al., 2010).

The mutation R249S is often found in human hepatocellular carcinomas associated with exposure to aflatoxin (as detailed below). A targeted mutation leading to the expression of a murine $p53^{R246S}$ (equivalent to human $p53^{R249S}$) has, so far, only been described in embryonic stem cells (Lee and Sabapathy, 2008): this revealed a dominant negative effect of the mutant protein. Transgenic $p53^{R246S}$ mice, described earlier, suggested that this mutant might act as a promoting agent for aflatoxin-induced hepatocarcinogenesis (Ghebranious and Sell, 1998).

The properties of this group of mutant proteins were also proposed to result from their increased propensity to aggregate. The mutants R175H, R249S and R282W could coaggregate, in the cytoplasm, with wild-type p53, p63 or p73, causing deficient induction of target genes (Xu et al., 2011).

Finally, p53 was recently found to facilitate the maturation of a subset of primary miRNAs, by forming a complex with Drosha and p68. p53 point mutations in the DNA binding domain, such as R175H and R273H, were shown to disrupt the interaction between Drosha and p68 and lead to attenuated miRNA processing, suggesting another oncogenic property acquired by these p53 mutants (Suzuki et al., 2009).

2.2 Mutations in other domains of p53

In vitro and transfection studies suggested that post-translational modifications in the transactivation domain (TAD), proline-rich domain (PRD) and C-terminal domain (CTD) are important for p53 activity. Although mutations affecting these domains are extremely rare in human cancers, mouse models carrying such mutations have provided insight into p53 regulation.

2.2.1 Mutations in the Transactivation Domain (TAD)

The N-terminal p53 TAD, containing the major site of interaction with Mdm2, was initially defined as encompassing the first 40 residues of the protein. Phosphorylation of serines in the TAD were thought to be crucial for p53 activation and stabilization, by preventing Mdm2 binding and promoting p300 binding, but when mutations of such residues were targeted at the murine locus and evaluated *in vivo*, unexpected phenotypes were observed. Mutations S18A or S23A (corresponding to human S15A and S20A respectively) independently led to no or mild alterations in p53 stability, transactivation, cell cycle control and apoptosis (Chao et al., 2003; Sluss et al., 2004; Wu et al., 2002). However $p53^{S18A,S23A}$ mice, carrying mutations of the two residues, were deficent in inducing apoptosis and developped various types of late onset tumors (Chao et al., 2006). Furthermore, transfection studies led to propose that human p53 mutations of leucine 22 and tryptophan 23 into glutamine and serine (L22Q and W23S) would disrupt Mdm2 interaction and prevent the recruitement of transcription co-activators, leading to a stabilized p53 protein with reduced transactivation capacity (Lin et al., 1994). This hypothesis was confirmed in a mouse model expressing the equivalent mutant protein $p53^{L25Q,W26S}$ (referred to as $p53^{25,26}$ below) : $p53^{25,26}$

protein was very stable due to the lack of Mdm2 binding, and its ability to transactivate target genes in response to acute DNA damage was impaired. Its increased stability and residual activity led to early embryonic lethality (Johnson et al., 2005).

The work of Zhu et al. led to propose the existence of a secondary TAD domain (TAD2), adjacent to the first TAD, roughly corresponding to residues 43 to 63 (Zhu et al., 1998). The role of the two transactivation domains was further studied in a recent work, which compared the $p53^{25,26}$ mouse model to the mouse $p53^{53,54}$, with 2 mutations in the TAD2 (L53Q and W54S), and to the quadruple mutant $p53^{25,26,53,54}$ (Brady et al., 2011) (Figure 3). The similarity of $p53^{53,54}$ MEFs, but not $p53^{25,26}$ nor $p53^{25,26,53,54}$ MEFs, to wild-type cells in target gene induction after acute genotoxic stress suggested that the p53 DNA damage response relies on an intact TAD1. However, in a model of *KrasG12D*–induced lung tumorigenesis, $p53^{25,26}$ could suppress tumor formation as efficiently as wild-type p53, whereas the quadruple mutant acted as a p53 null protein. Thus, an intact TAD1 is required to achieve an acute genotoxic response, but TAD1 and TAD2 can function redundantly to supress tumors. This may explain why mutations in the TAD are rare in human cancers.

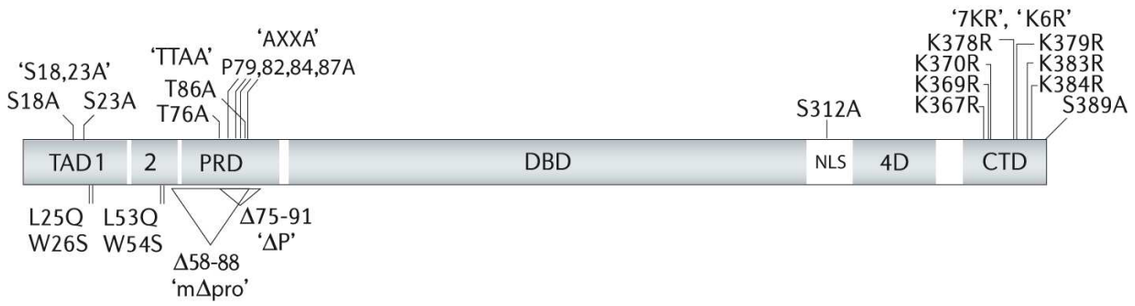


Fig. 3. Schematic representation of the murine p53 protein and the targeted mutations (outside of the DNA binding domain) that were generated. TAD (1 & 2): transactivation domain ; PRD : proline-rich domain ; DBD : DNA binding domain ; NLS : nuclear localization signal ; 4D : tetramerization domain ; CTD : C-terminal domain (Modified from Toledo and Wahl, 2006).

2.2.2 Mutations in the Proline-Rich Domain (PRD)

Human p53 lacking residues 62-91 in the PRD was found to be more sentitive to Mdm2-mediated degradation, and this was proposed to result from the loss of an essential prolyl isomerase PIN1 binding site within the PRD (Berger et al., 2005; Berger et al., 2001; Dumaz et al., 2001). The PRD might also ensure optimal p53-p300 interactions through PXXP motifs (Dornan et al., 2003). Consistent with *in vitro* findings, mouse model $p53^{\Delta P}$, lacking the amino acids 75-91 with all PXXP motifs and putative PIN1 sites deleted, displayed reduced protein stability and transactivation capacity (Toledo et al., 2006). However, $p53^{\Delta P}$ was deficient in cell-cycle control but retained a partial pro-apoptotic capacity, in striking contrast to what transfection studies had suggested. This surprising phenotype was confirmed by the observation that $p53^{\Delta P}$ rescues Mdm4-null but not Mdm2-null embryos. Another mouse model of the PRD, $p53^{m\Delta pro}$, expressing a p53 lacking residues 58-88, was reported later (Slatter et al., 2010). $p53^{m\Delta pro}$ retained a capacity to control the cell cycle in bone marrow cells, but it was not analyzed in MEFs like the $p53^{\Delta P}$ mutant, and attempts to

rescue Mdm2-null or Mdm4-null embryos were not performed in a $p53^{m^{\Delta}pro}$ context. Thus, further analyses are needed to evaluate the similarities or differences between the $p53^{\Delta P}$ and $p53^{m^{\Delta}pro}$ mutants.

Mouse mutants with more subtle mutations in the PRD were also reported (Toledo et al., 2007). $p53^{TTAA}$, with threonines 76 and 86 mutated into alanines, removed only the putative PIN1 binding sites in the PRD. These mutations partially affected p53 stabilization upon DNA damage, but the mutant protein remained as active as wild-type p53, suggesting that PIN1 binding sites in the PRD participate in p53 stability control, but exert little effects on p53 function. In the mutant $p53^{AXXA}$, prolines 79, 82, 84 and 87 were mutated into alanines, to remove both PXXP motifs of the murine p53 PRD. The stability and activity of this mutant did not differ significantly from that of WT p53, suggesting either that the PRD has mainly a structural role, or that PXXXXP motifs present in the $p53^{AXXA}$ protein are sufficient to ensure protein-protein interactions.

2.2.3 Mutations in the C-terminal region of the protein

Several kinases may phosphorylate serines 315 and 392 in human p53. Unlike other serines or threonines in p53 that are phosphorylated by stress-related kinases, serine 315 is predominantly phosphorylated by cell cycle-related kinases. Furthermore, whether this phosphorylation regulates p53 functions positively or negatively appeared controversial after *in vitro* studies (Fogal et al., 2005; Qu et al., 2004; Zacchi et al., 2002; Zheng et al., 2002). Two mouse models expressing $p53^{S312A}$ (equivalent to a S315A mutation in human p53) were recently reported (Lee et al., 2010; Slee et al., 2010). This mutation did not affect the survival of mice under normal physiological conditions and appeared to have only mild effects on stress-responses in fibroblasts. However, the irradiation of $p53^{S312A/S312A}$ mice revealed their predisposition to develop thymic lymphomas and liver tumors, and a decreased p53 response was demonstrated in liver tumors (Slee et al., 2010). As for serine 392, *in vitro* studies revealed its phosphorylation in response to UV irradiation, correlated with p53 activation (Kapoor and Lozano, 1998; Lu et al., 1998). Mice with an equivalent mutation (S389A) were resistant to spontaneous tumors with a normal p53 stability, but presented a slightly reduced apoptotic response after UV irradiation, and a slightly higher UV-induced skin tumor occurrence (Bruins et al., 2004).

Human p53 contains 6 lysine residues in its C-terminal domain, subjected to various post-translational modifications including acetylations and ubiquitinations, long thought to be crucial for the regulation of p53 protein activity and stability (Nakamura et al., 2000; Rodriguez et al., 2000). However, mouse models expressing a p53 with 6 or 7 C-terminal lysines mutated into arginines (referred to as $p53^{K6R}$ or $p53^{7KR}$, respectively) appeared rather similar to wild-type mice, suggesting that these residues only participate in the fine-tuning of p53 responses (Feng et al., 2005; Krummel et al., 2005). More recently, $p53^{7KR}$ mice were found to be hypersensitive to γ-irradiation, due to defects in hematopoiesis (Wang et al., 2011).

2.2.4 Mutations in non-coding regions

Cancer related-mutations in intronic sequences were not studied as extensively as those in exons. Mutations in non-coding regions may affect splicing sites, potentially resulting in truncated protein products or reduced protein levels (Holmila et al., 2003). For example, an

A-to-G transition in intron 10 that eliminates a splicing acceptor site and causes a frameshift was recently reported in a pediatric adenocortical tumor (Pinto et al., 2011). *In silico* analyses suggested that the resulting mutant protein may be misfolded or may aggregate, accounting for a loss in tumor suppressor capacity.

3. p53 mutations and the etiology of human cancers

The distribution of *TP53* missense mutations in human cancers correlates with their functional impact, as the most frequent mutations severely impair sequence-specific DNA binding and transactivation. Importantly, the frequencies and types of mutations in *TP53* reflect both the selective growth advantage they confer to mutated cells, and the mutability of a particular codon to endogenous metabolites or exogenous carcinogens. Spontaneous deamination and environmental carcinogens are considered to be the main sources of mutagenesis.

3.1 Spontaneous C to T transversion

CpG dinucleotides in *TP53* are highly methylated in normal tissues, and the 5'-methylated cytosine undergoes spontaneous deamination at a higher rate than an unmethylated base, leading to a cytosine to thymidine transition. 33% of *TP53* DBD mutations occur at methylated CpG sites, affecting 5 major hotspot mutations (codons 175, 245, 248, 273 and 282), and this is considered as a main source of internal cancers (Gonzalgo and Jones, 1997).

3.2 Mutations induced by exogenous carcinogens

3.2.1 Aflatoxin & p53R249S mutations

The incidence of hepatocellular carcinoma (HCC) correlates well with the occurrence of two principal etiologic factors : hepatitis B or C infections and exposure to aflatoxins in the diet, causing a G to T transversion at codon 249 (R249S) (Aguilar et al., 1993). In high incidence areas for HCC, the molds *Aspergillus flavis* and *Aspergillus parasiticum* contaminate maize and peanuts producing aflatoxins that, once metabolized by the liver, may generate DNA adducts at several guanines in *TP53*, leading to G to T transversions. In fact, the aflatoxin adducts occur at a few codons, and the high frequency of R249S (AGG ➔ AGT) mutation results from its clonal selection during hepatocellular carcinogenesis.

3.2.2 Smoking & lung cancer

p53 mutations are common in lung cancers, with a frequency of 75% in smokers, showing a strong correlation between smoking and p53 mutations. Human lung cancers from smokers display a distinct *TP53* mutation pattern with a predominant G to T/A transversion, whereas C to T transitions are enriched in other cancer types. These smoking-induced transversions, caused by the benzo(a)pyrene metabolites in the tobacco smoke, are often observed in methylated CpG sequences at codons 157, 158, 245, 248 and 273 (Le Calvez et al., 2005). Intriguingly, the majority of G to T transversions occur on the nontranscribed strand, suggesting that the benzo(a)pyrene adducts on that strand are less efficiently removed. Thus, the distribution of *TP53* mutations in lung cancers results from the combined effects of site preference for adduct formation, differential DNA strand repair efficiencies, and clonal selection of the mutations that most affect p53 function.

3.2.3 UV & skin carcinomas

The major cause of nonmelanoma skin cancers is sunlight. In basal and squamous cell skin carcinomas, a high frequency of C to T transitions in *TP53* is observed, including tandem CC to TT transitions, considered to be the mutagen fingerprint of ultra-violet (UV) irradiation. The tandem CC to TT transitions would result from UV-induced pyrimidine dimers that escape nucleotide excision repair (NER). Consistent with this, skin tumors from *Xeroderma pigmentosum* patients, deficient in NER, exhibit a high frequency of CC to TT transitions in tumor suppressor genes such as *TP53* and *PTCH1* (Bodak et al., 1999). Importantly, the mutagen fingerprint of UV on the *TP53* gene suggests that farmers, fishermen and forestry workers are predisposed to basal cell skin carcinomas because of their occupational exposure to sunlight (Weihrauch et al., 2002).

4. Effects of Single Nucleotide Polymorphisms (SNPs) in the p53 pathway

By definition, a single nucleotide polymorphisms (SNP) affects at least 1% of a population. Numerous SNPs are present at the *TP53* locus and in genes involved in the p53 network. They may increase cancer risk and affect response to therapeutic regimens.

4.1 SNPs in *TP53* and *TP73*

4.1.1 Codon 72 Pro/Arg

The most studied SNP in *TP53* is the Proline/Arginine variation at codon 72 (referred to as p53-72Pro or p53-72Arg, respectively). This SNP is due to a change in the DNA sequence encoding the proline-rich domain of p53 (CCC or CGC). Experiments in human cell lines have suggested that the variant p53-72Arg is more efficient in inducing apoptosis, whereas p53-72Pro would be more efficent in transactivating p21 and inducing cell cycle arrest (Dumont et al., 2003; Pim and Banks, 2004; Salvioli et al., 2005; Sullivan et al., 2004). Studies of the association of these polymorphic variants with cancer risk have been controversial however (Whibley et al., 2009). Several models of 'humanized' mice designed to reproduce the p53-72Pro/Arg polymorphism were recently reported (Azzam et al., 2011; Frank et al., 2011; Zhu et al., 2010). These models revealed tissue-specific effects of the codon 72-polymorphism, which may explain the controversial findings in human studies.

4.1.2 Codon 47 Pro/Ser

The SNP p53-47 Proline or Serine (referred to as p53-47Pro or p53-47Ser hereafter), resulting from a C to T substitution at position 1 of codon 47, has been reported in populations of African origin (Felley-Bosco et al., 1993). The variant p53-47Ser, which was described to decrease the induction of some pro-apopotic genes by reducing the phosphorylation level at the adjacent serine 46 residue (Li et al., 2005), deserves further investigation.

4.1.3 Codon 217 Val/Met and codon 360 Gly/Ala

The SNP p53-217 Valine/Methionine is the only polymorphism found in the p53 DBD, which could be expected to affect p53 activity. Its function has only been tested in yeast and the p53-217Met variant showed an increased transactivation capacity (Kato et al., 2003). The SNP p53-360 Glycine/Alanine is located in the linker region adjacent to the p53 4D, and a

yeast assay indicated that induction of some p53 target genes are slightly decreased with the p53-360Ala variant (Kato et al., 2003). Further studies of these SNPs in a mammalian system are required to address their role in human cancers.

Importantly, additionnal SNPs that appear specific to Chinese populations were recently reported, but their impact on cancer risk remains to be evaluated in large cohorts (Phang et al., 2011). SNPs that could influence cancer risk need to be precisely evaluated in other p53 family members as well. At present, one SNP likely relevant for cancer research has been found in *TP73*. Table 1 summarizes the identified SNPs in members of the p53 family.

Gene	Function	SNP	Molecular description	Clinical association
TP53	Tumor suppressor, transcription factor ; induces cell cycle arrest and apoptosis in response to stress	72Arg/Pro 47Pro/Ser 217Val/Met 360Gly/Ala	See text	
TP73	Transactivates p53 target genes, some isoforms inhibit p53 functions	G4C14/ A4T14	Two linked intronic SNPs, upstream of the translation starting site in position 4 and 14	A4T14 allele : increased risk of squamous cell carcinoma of the head and neck, gastric, colorectal and endometrial cancers ; G4C14 allele : increased risk of lung cancer in Chinese population

Table 1. Cancer-related SNPs in the p53 family. Data collected from (Chen et al., 2008; De Feo et al., 2009; Hu et al., 2005; Kaghad et al., 1997; Niwa et al., 2005; Pfeifer et al., 2005).

4.2 SNPs in the p53 pathway

Genes encoding p53 regulators, and p53 target genes also exhibit single nucleotide polymorphisms, which may affect p53 responses and synergize with SNPs or mutations in *TP53* to alter cancer risk and clinical outcome. The current informations on SNPs in p53 regulators and p53 target genes are summarized in Tables 2 and 3 respectively.

5. Future perspectives : The importance of p53 isoforms

Recent studies have shown that *TP53* has a complex gene structure, much like the genes encoding its family members p63 and p73. Human *TP53* encodes 12 isoforms due to the presence of multiple promoters, translation initiation sites and alternative sites of splicing (Bourdon et al., 2005; Marcel et al., 2010a). These isoforms are expressed in normal tissues in a tissue-specific manner, and at least some of them appear to participate in the regulation of full length-p53 (FL-p53) and to play a role in tumor progression (Bourdon, 2007).

The 12 human p53 protein isoforms are illustrated in Figure 4. Δ40p53, an isoform lacking the first transactivation domain (TAD1), can be obtained by alternative splicing of intron 2 or by the use of alternative translation initiation (Courtois et al., 2002; Ghosh et al., 2004; Ray et al., 2006). Under endoplasmic reticulum (ER) stress, Δ40p53 expression is increased,

Gene	Function	SNP	Molecular description	Clinical association
Mdm2	Regulates p53 stability	SNP309	T/G in intron 1. G creates a Sp1 binding site, increasing Mdm2 expression	G : increased risk for early onset tumors, particularly in young females
Mdm4	Regulates p53 activity	SNP34091	A/C in the 3'UTR region. Mdm4-C allele is a target of hsa-miR-191 but not Mdm4-A	C : later onset of ovarian carcinomas and increased response to chemotherapy
ATM	Phosphorylates and activates p53 upon DNA damage	1853 Asp/Asn	Asp or Asn at codon 1853. Asn leads to decreased activation of p53	Asn : increased colorectal cancer risk and reduced melanoma risk
NQO1	Stabilizes p53 upon oxidative stress	187 Pro/Ser	Pro or Ser at codon 187. Ser leads to loss of activity	Ser : increased cancer risk

Table 2. Cancer-related SNPs in regulators of p53. Summarized data for SNPs in Mdm2 (Bond et al., 2004; Bond and Levine, 2007; Post et al., 2010), Mdm4 (Wynendaele et al., 2010), ATM (Barrett et al., 2011; Jones et al., 2005; Maillet et al., 1999; Thorstenson et al., 2001), NQO1 (Asher and Shaul, 2005; Jamieson et al., 2007; Ross and Siegel, 2004).

Gene	Function	SNP	Molecular description	Clinical association
CDKN1A (p21)	Regulator of G1-S cell cycle progression	31 Ser/Arg	Ser or Arg at codon 31	Ser : increased esophageal, breast cancer risk ; Arg : increased type-C chronic lymphocytic leukemia
CDKN1B (p27)	Regulates cell cycle	-79C/T	C/T in 5'UTR, 79 nt upstream of the translation start site	T : increased prostate, breast, thyroid cancer risk
BAX	pro-apoptotic	-125 G/A	G/A in the promoter, 125 nt before transcription start site	A : increased risk for head and neck carcinomas and chronic lymphocytic leukemia
CASP8	pro-apoptotic	302 Asp/His	Asp or His at codon 302	His : reduced breast cancer incidence

Table 3. Cancer-related SNPs in p53 target genes. Summarized data for SNPs in p21 (Ebner et al., 2010; Johnson et al., 2009; Yang et al., 2010), p27 (Chang et al., 2004; Driver et al., 2008; Landa et al., 2010; Ma et al., 2006), Bax (Chen et al., 2007; Lahiri et al., 2007), Caspase 8 (Cox et al., 2007; MacPherson et al., 2004; Palanca Suela et al., 2009).

leading to G2 arrest (Bourougaa et al., 2010). Transgenic mice overexpressing Δ40p53 exhibit an increased cellular senescence, a slower growth rate, memory loss, neurodegeneration and accelerated ageing (Maier et al., 2004; Pehar et al., 2010).

Δ133p53 and Δ160p53 isoforms are expressed from an evolutionary conserved promoter located in intron 4 (Bourdon et al., 2005). Studies in human cells and zebrafish indicated that this internal promoter is transactivated by FL-p53 (Aoubala et al., 2011; Chen et al., 2009; Marcel et al., 2010b). Human Δ133p53 and zebrafish Δ113p53, isoforms lacking the TAD and part of the DBD, have an anti-apoptotic role (Bourdon et al., 2005; Chen et al., 2009). In addition, overexpression of Δ133p53 was found to extend cellular replicative lifespan by inhibiting p21 and miR-34 (Fujita et al., 2009). Δ133p53 is absent in normal mammary tissues, but present in breast cancers, and its overexpression is correlated with the progression of colon cancer from adenomas to carcinomas. The Δ160p53 isoform results from an alternative translation intiation site, within the same mRNA transcript that encodes Δ133p53 (Marcel et al., 2010a). The function of this isoform, identified very recently, is presently unknown.

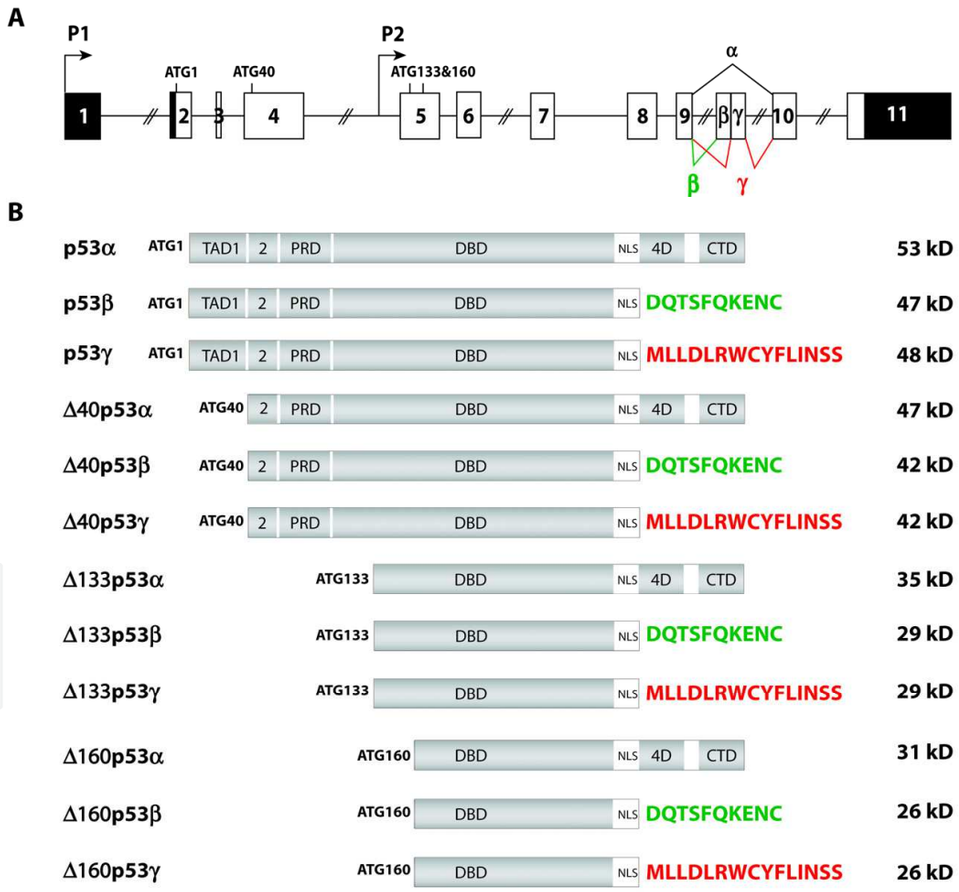


Fig. 4. *TP53* encodes 12 putative isoforms. (**A**) *TP53* gene structure with 2 promoters (P1 and P2), 4 translation initiation sites (ATG1, ATG40, ATG133 and ATG160) and 3 C-terminal alternative splicing sites (α, β and γ). (**B**) 12 protein isoforms of human p53 with their name and molecular weight listed on the left and right, respectively. The functional domains and the specific C-terminal sequences for the β and γ variants are indicated.

The use of alternative splicing sites in intron 9 results in the production of 2 isoforms with distinct C-terminal domains : p53β and p53γ (Bourdon et al., 2005). These 2 isoforms lack the oligomerization domain, but are proposed to work independently of FL-p53 by transactivating p53 target genes in a promoter-specific manner, or together with FL-p53 to modulate its target gene expression. Luciferase assays indicated that p53β could increase p53-dependent expression of *p21*, consistent with the observation that p53β cooperates with FL-p53 to accelerate replicative senescence of human fibroblasts (Fujita et al., 2009). p53γ may enhance p53 transcriptional activity on the *BAX* promoter (Bourdon et al., 2005). In a study of 127 randomly selected primary breast tumors, the expression of the p53β and p53γ were found to associate with oestrogen receptor (ER) expression and mutation of *TP53* gene, respectively (Bourdon et al., 2011). Patients expressing only mutant p53 had a poor prognosis, as expected. Interestingly however, patients with mutations in *TP53* expressing p53γ had low cancer recurrence and an overall survival as good as that of patients with wild-type p53. These results suggest that the expression status of p53 isoforms should be precisely determined in human cancers, to evaluate their relevance in cancer therapy and prognosis. Consequently, it becomes important to determine the impact of each point mutation in *TP53* on the synthesis of p53 isoforms.

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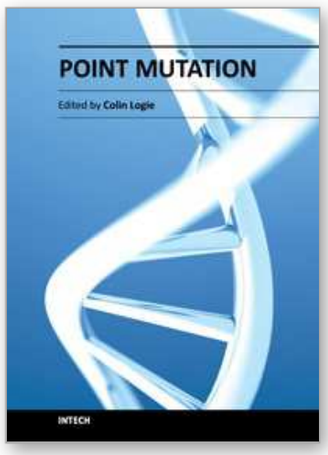
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This book concerns the signatures left behind in chromosomes by the forces that drive DNA code evolution in the form of DNA nucleotide substitutions. Since the genetic code predetermines the molecular basis of life, it could have been about any aspect of biology. As it happens, it is largely about recent adaptation of pathogens and their human host. Nine chapters are medically oriented, two are bioinformatics-oriented and one is technological, describing the state of the art in synthetic point mutagenesis. What stands out in this book is the increasing rate at which DNA data has been amassed in the course of the past decade and how knowledge in this vibrant research field is currently being translated in the medical world.

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