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A mouse model of the Δ133p53 isoform: roles in cancer progression and inflammation

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Abstract
This review paper outlines studies on the Δ122p53 mouse, a model of the human Δ133p53 isoform, together with studies in other model organisms, cell culture, and where available, clinical investigations. In general, these studies imply that, in contrast to the canonical p53 tumor suppressor, Δ133p53 family members have oncogenic capability. Δ122p53 is multifunctional, conferring survival and proliferative advantages on cells, promoting invasion, metastasis and vascularization, as does Δ133p53. Cancers with high levels of Δ133p53 often have poor prognosis. Δ122p53 mediates its effects through the JAK–STAT and RhoA–ROCK signaling pathways. We propose that Δ133p53 isoforms have evolved as inflammatory signaling molecules to deal with the consequent tissue damage of p53 activation. However, if sustained expression of the isoforms occur, pathologies may result.

The p53 tumor suppressor

The tumor suppressor protein p53 plays a key role in preventing cancer. p53 is normally expressed at low concentrations due to binding the ubiquitin E3 ligase mouse double minute 2 homolog (MDM2) that mediates its degradation (Kubbutat et al. 1997). However, when a cell is exposed to stress stimuli such as DNA damage or oncogene activation, p53 is released from MDM2 and the concentration of p53 rises dramatically (Kubbutat et al. 1997). Once activated, p53 facilitates cell death or an arrest of cell division to facilitate repair, thus preventing cells with a damaged genome from replicating [reviewed in (Horn and Vousden 2007; Fischer 2017)]. These various responses rely primarily on p53 functioning as a transcription factor that regulates stress response genes, such as cyclin-dependent kinase inhibitor 1a (*Cdkn1a*/p21) (el-Deiry et al. 1993, 1995), BCL2-associated X protein (*Bax*) and BCL2 binding component 3 (*BBC3*/Puma) (Nakano and Vousden 2001). In recent years, additional roles for p53 have been established with p53 supporting autophagy, development, innate and adaptive immune responses [reviewed in (Munoz-Fontela et al. 2016; Yang and Karin 2014; Lowe et al. 2013)], and fundamental metabolic events including amino acid and glucose metabolism (Kruiswijk et al. 2015). Canonical metastasis pathways, including cell adhesion, motility, invasion, extracellular matrix (ECM) interactions, epithelial–mesenchymal transition (EMT), stemness, anoikis, and angiogenesis are also largely down-regulated by p53 [reviewed in (Powell et al. 2014; Teodoro et al. 2007)]. All these biological activities of p53 may contribute to its tumor suppressor functions.

By contrast, loss of wild-type (WT) p53 function promotes cancer. Mice deleted for the p53 gene (*Trp53*) are highly tumor prone (Donehower et al. 1992) and in Li–Fraumeni syndrome (LFS) where mutations in the *TP53* gene are inherited, multiple tumor types occur (Malkin et al. 1990). Furthermore, inactivation of p53 by missense mutations, or by interaction with inhibitory proteins [e.g., E6 from Human Papillomavirus (Mighty and Laimins 2014)], is a frequent event in human cancer. Despite this, identifying *TP53* mutations alone has limited power in predicting patient outcome (Bourdon et al. 2005; Machado-Silva et al. 2010).

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Human p53 isoforms

In the last decade, an additional layer of p53 regulatory mechanism has emerged through the discovery of at least 13 isoforms of p53: TAp53 (α, β, γ), Δ40p53 (α, β, γ), Δ133p53 (α, β, γ), Δ160p53 (α, β, γ), and p53ψ, produced by the use of alternative promoters [a distal promoter (P1): TA, and an internal promoter (P2): Δ133p53], splicing (intron 2: Δ40p53; intron 6: p53ψ; and intron 9: α, β, and γ), and alternative sites of translation (Δ40p53 and Δ160p53) (Bourdon et al. 2005; Marcel et al. 2010; Senturk et al. 2014) (Fig. 1).

Δ40p53 isoforms can be produced from two mRNAs FL/Δ40TP53_T1 and FL/Δ40TP53_T2 (Fig. 1a) by internal initiation of translation, through an internal ribosomal entry site (IRES) in the 5′ UTR of the transcript (Sharathchandra et al. 2014). These transcripts differ by only three nucleotides, due to the incorporation of CAG at the intron/exon two junction (Mehta et al. 2016). It has been also been shown that a G-quadruplex structure in intron 3 regulates splicing of intron 2, and the mRNA that retains intron 2 encodes for Δ40p53 (Marcel et al. 2011a).

The three Δ133p53 isoforms (Δ133p53α, Δ133p53β, Δ133p53γ) lack the first 132 amino acids of WT p53, corresponding to the loss of the transactivation domain (TAD), the MDM2 binding site, the proline-rich domain (PrD), and a small part of the DNA binding domain (DBD) (Bourdon et al. 2005). These are transcribed from an internal promoter (P2) in intron 4 (Fig. 1). The β and γ isoforms lack part of the canonical *C*-terminal oligomerisation domain of p53, due to a stop codon in exon 9b, terminating with 10 or 15 additional amino acids (Khoury and Bourdon 2011) (Fig. 1b).

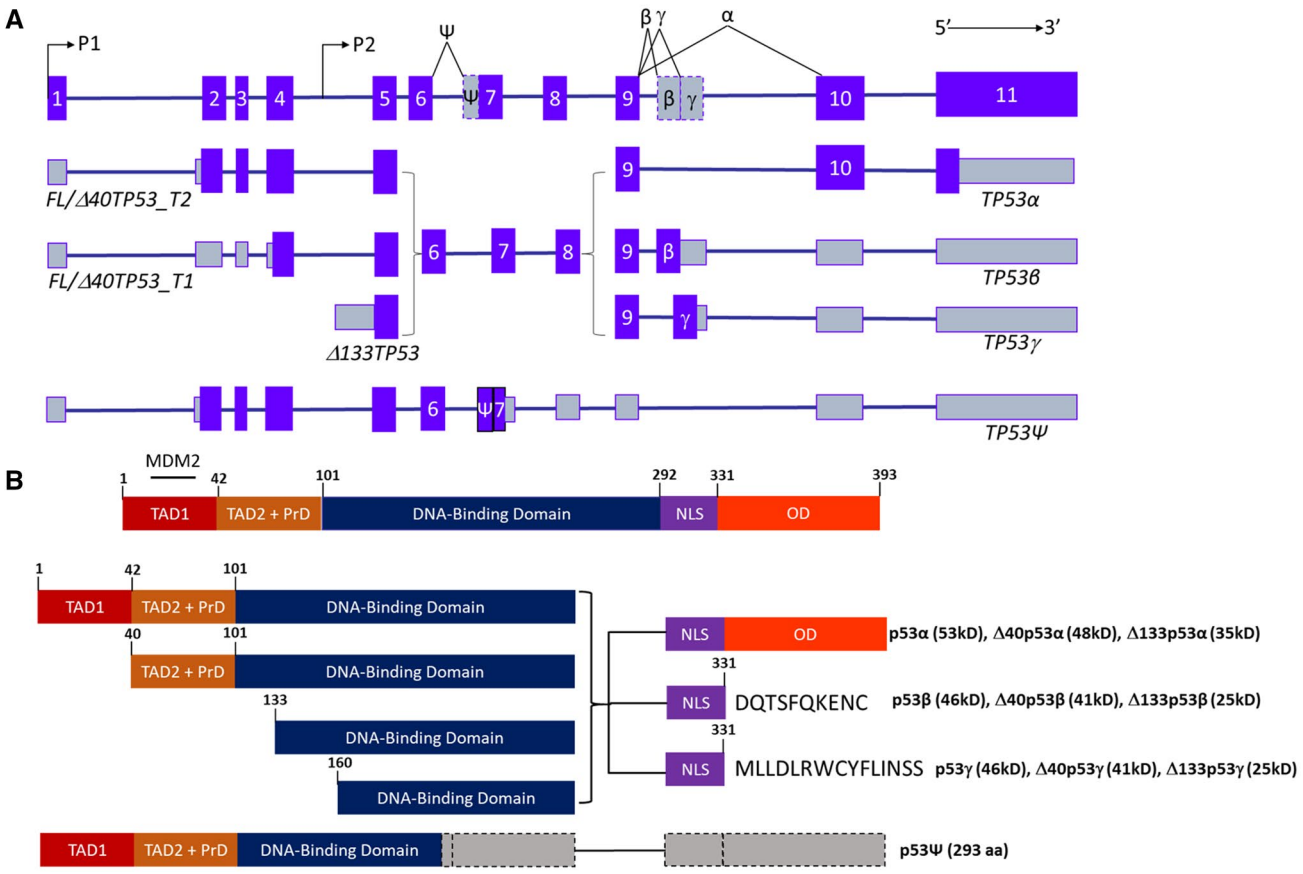

Fig. 1 Human *TP53* gene, known RNA transcripts and protein isoforms. **a** Schematic demonstrating the *TP53* gene locus and the 10 *TP53* RNA transcripts known to be generated by alternative splicing and alternative promoter usage (P1 and P2). At the top of the figure, exons are numbered and illustrated in purple, with the regions of supplementary exons either 6Ψ and 9β or 9γ that are included in the alternatively spliced transcripts Ψ, β, and γ variants, shown in gray. **b** Schematic of the canonical p53 protein and the 13 known isoforms. *TAD*1 Transactivation domain 1, *TAD*2 Transactivation domain 2, *PrD* Proline-rich domain, *NLS* nuclear localization signal, *OD* Oligomerization domain, *MDM*2 binding site for MDM2

Conservation of p53 isoforms

The dual gene structure of the p53 gene is conserved across different species, including Drosophila, zebrafish, mouse, and man [reviewed in (Khoury and Bourdon 2011; Marcel et al. 2011b)]. The Drosophila (*D*)*p53* gene encodes full-length Dp53 and DΔNp53 by alternative translational initiation, that is homologous to Δ40p53, but there is no equivalent of Δ133p53 (Marcel et al. 2011b). The zebrafish p53 gene (*Zp53*) also encodes full-length Zp53, ZΔNp53, and from an internal promoter, a transcript that leads to the expression of *Δ113p53*, encoding for an *N*-terminally truncated p53 protein initiated at codon 113, homologous to Δ133p53α (Chen et al. 2005).

The mouse p53 gene (*Trp53*/*Mp53*) encodes full-length Mp53 and five Mp53 variants [Fig. 2a, b; reviewed in (Marcel et al. 2011b)]. Two *N*-terminally truncated variants have been described: the MΔ41p53 isoform (also named ΔNp53 or p44) results from alternative initiation of translation at codon 41 (Wolf et al. 1985). A second variant is transcribed from an internal promoter within intron 4 of the mouse *Trp53* gene, similar to Δ133p53. However, the only predicted protein is MΔ157p53, equivalent to the human Δ160p53 isoform (Marcel et al. 2011b), due to the absence of a methionine at the equivalent position to Δ133p53. In addition, an alternative splicing event using a cryptic 3′ splicing site in intron 10, located 96 bp upstream of the regular 3′ splicing site of exon 11 leads to the production of a truncated p53 protein, named Mp53AS (Wolf et al. 1985; Arai et al. 1986). The Mp53AS isoform has the last 26 amino acids of mouse p53 replaced by 17 new amino acids homologous to human β peptide of p53 (Wolf et al. 1985; Arai et al. 1986). Both MΔ41p53 and MΔ157p53 are expressed as *C*-terminal AS variants (Khoury and Bourdon 2011; Marcel et al. 2011b) (Fig. 2b).

A mouse model of the Δ40p53 isoform

To study the functions of the Δ40p53 in vivo, a mouse was constructed in which Δ40p53 was introduced into a p53-null mouse background (Maier et al. 2004). Overexpression of Δ40p53 did not produce a unique tumor phenotype, with tumors appearing at the same rate and of the same type as p53-null mice (Maier et al. 2004). However, when co-expressed with WT p53, Δ40p53 increased insulin-like growth factor (IGF)-1 resulting in an accelerated aging phenotype (Maier et al. 2004). Thus, it appears that Δ40p53 has no phenotype except when co-expressed with WT p53.

A mouse model of the Δ133p53 isoform

In a similar vein, we generated a mouse expressing an *N*-terminal deletion similar to the Δ133p53 isoforms (designated Δ122p53), providing the first mouse model of the Δ133p53 isoform (Slatter et al. 2011; Campbell et al. 2012). The mutant Δ122p53 open reading frame (ORF) requires the use of an alternative translational start site 74 bp downstream of the normal start site and correct splicing between exon 2 and the last amino acid of exon 4 (Slatter et al. 2011) (Fig. 2c). Two transcripts can be generated due to alternate splicing of exons 10 and 11 to generate Δ122p53α and Δ122p53AS, said to be equivalent to Δ133p53β (Wolf et al. 1985; Arai et al. 1986) (Fig. 2d). Similar to Δ133p53, Δ122p53 proteins lack both TADs, the MDM2 binding site, the PrD, and part of the DBD. Thus, Δ122p53 should mimic the functions of Δ133p53 proteins, but not the transcriptional regulation of the *Δ133TP53* gene. As *C*-terminal splicing still occurs in Δ122p53, the phenotypes described below could be due to one or both of Δ122p53α and Δ122p53AS.

Characteristics of Δ122p53 mice

Δ122p53 mice are developmentally impaired

The Δ122p53 mice do not breed well. In one cohort study carried out with 520 animals, only 86 live offspring were produced comprising 18 females and 68 males (Slatter et al. 2011, 2015). The reduced frequency of females is in part due to exencephaly in the embryos similar to p53-null mice, but other abnormalities were also observed. These include hydrocephalus in female mice, unilateral or bilateral anophthalmia or microphthalmia (missing or small eyes) mostly in female mice, kinked tail due to additional vertebrae, and more cases of fetal reabsorption. These abnormalities have not been quantitated but they suggest that Δ122p53 contributes to multiple developmental processes. A role in development has also been reported for the ZΔ113p53 (Chen et al. 2005). In a zebrafish mutant characterized by restrictive digestive organ growth, ZΔ113p53 was increased and functioned to moderate transcription of Zp53 response genes, resulting in an arrest of cell proliferation (Chen et al. 2005). Most effects of ZΔ113p53 appear to result from modulation of Zp53 (Chen et al. 2005, 2009). Drosophila DNp53 also plays a role in development/differentiation by controlling cell death and division (Fan et al. 2010; Brodsky et al. 2004, 2000; Ollmann et al. 2000).

Δ122p53 mice are tumor prone

Δ122p53 mice are highly tumor prone and have a distinct tumor spectrum (Slatter et al. 2011). Homozygous Δ122p53 had a ~ 30% shorter lifespan than p53-null mice (median

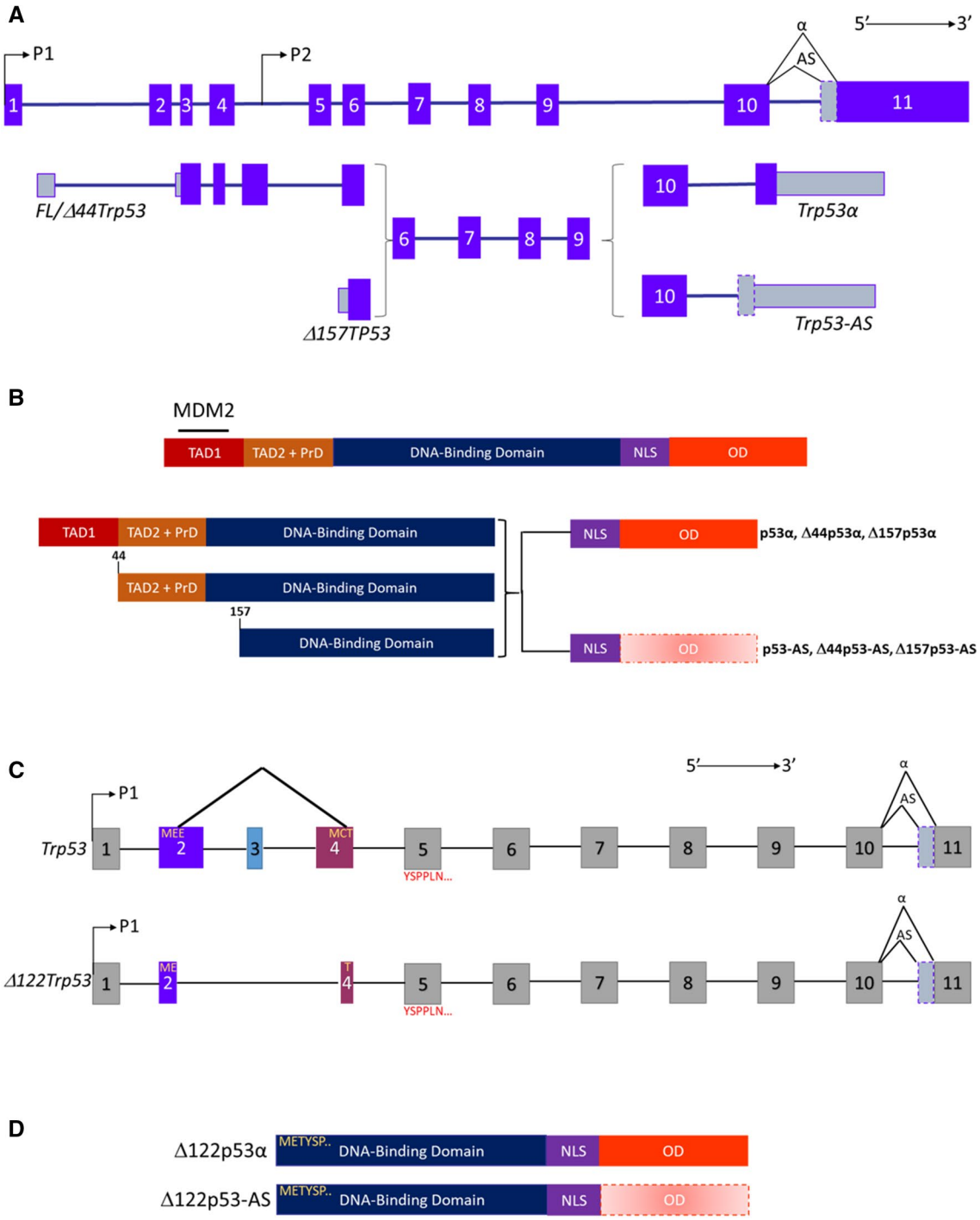

Fig. 2 Schematic of *Trp53* gene and the N-terminal mutant Δ122p53 gene, RNA transcripts and protein isoforms. **a** Illustrating the *Trp53* gene locus and the 4 *Trp53* RNA transcripts known to be generated by alternative splicing and alternative promoter usage (P1 and P2). At the top of the figure, exons are numbered and illustrated in purple, with the 3′ alternatively spliced AS variants shown in a dotted gray box. **b** Shows the canonical mouse p53 protein and the 6 known isoforms. **c** Shows the *Trp53* gene and the deletion between exon 2 and exon 4 to produce the *N*-terminal mutant Δ122p53 gene. The Δ122p53 RNA transcripts are generated using the P1 promoter. The exons are numbered and illustrated in gray, with the exons spliced to generate the Δ122p53 transcript colored, the 3′ alternatively spliced AS variant is shown in dotted gray boxes. **d** Shows the protein isoforms coded by the Δ122p53 transcript. *TAD*1 Transactivation domain 1, *TAD*2 Trans-activation domain 2, *PrD* Proline-rich domain, *NLS* nuclear localization signal, *OD* Oligomerization domain, *MDM*2 binding site for MDM2

survival 111 days compared with 149 days in p53-null mice) and similarly, mice heterozygous for the WT p53 allele and Δ122p53 ($p53^{+/\Delta122p53}$) develop tumors and had a reduced survival compared to mice with one WT and one p53-null allele ($p53^{+/-}$) (Slatter et al. 2011). Adding to evidence that the Δ122p53 allele is cancer promoting, malignant tumors from $p53^{+/\Delta122p53}$ mice retained both WT and Δ122p53 alleles (Slatter et al. 2011, 2015). In the Δ122p53 model, only benign tumors lost the Δ122p53 allele. This is distinct from tumors from $p53^{+/-}$ mice where the wild-type allele is often lost (Donehower et al. 1992). These data suggest 'co-operativity' between WT p53 and Δ122p53. The Δ122p53 mice also have a unique tumor spectrum with a high incidence of an aggressive disseminated B-cell tumor (diffuse large B-cell lymphomas, DLBCL) compared to thymomas that are predominant in p53-null mice (Donehower et al. 1992, 1995; Slatter et al. 2011).

Δ122p53 tumors have reduced apoptosis and increased cell proliferation

Consistent with a pro-tumorigenic phenotype, hematopoietic cells from Δ122p53 mice were defective for apoptosis and cell cycle arrest in response to DNA damage, and under physiological conditions, multiple tissues had more proliferating cells than in WT or p53-null mice (Slatter et al. 2011). Moreover, more colonies formed from bone marrow of Δ122p53 mice compared to other genotypes (Slatter et al. 2011) and p53-null cells engineered to express Δ122p53 showed a faster division time (Roth et al. 2016), so the increased proliferation is not simply due to inactivating WT p53.

Microarray analysis of splenocytes from Δ122p53 mice showed elevated expression of transcripts of pro-proliferative genes, such as *baculoviral inhibitor of apoptosis repeat-containing* 5 (*Birc5*/survivin) and *polo-like kinases 1* (*Plk1*) (Watanuki-Miyauchi et al. 2005; Liu et al. 2007), which are known to be markers of DLBCL subtypes having higher risk of relapsed or refractory disease (Liu et al. 2007; Hong et al. 2017). Δ122p53 was also found to be defective in the regulation of many p53 target transcripts including *Cdkn1a*/p21, *Bax*, and *Bbc3*/Puma genes (Slatter et al. 2011), suggesting Δ122p53 has distinct functions from WT p53. Proteomic analysis of peripheral blood mononuclear cells (PBMC) from Δ122p53 mice also showed elevated levels of pro-proliferation and anti-apoptotic proteins, including increased transgelin, translationally controlled tumor protein, and valosin-containing protein (Sawhney et al. 2015; Telerman and Amson 2009; Zhou et al. 2018; Fu et al. 2016).

In confirmation of these observations, Δ133p53 extended the lifespan of $CD8^+/CD28^-$ lymphocytes and rescued them from senescence (Mondal et al. 2013). Recent research has shown that Δ133p53β is involved in regulating the apoptotic response in colorectal cancer cell lines through suppression of the RhoB tumor-suppressive and pro-apoptotic activity (Arsic et al. 2017). In other studies, co-transfection of full-length p53 with Δ133p53 in p53-null H1299 cells impaired p53-induced apoptosis (Bourdon et al. 2005) and Δ133p53α inhibited replicative senescence (Fujita et al. 2009) and G1 cell cycle arrest by reducing the ability of WT p53 to regulate its target genes, including *Cdkn1a*/p21 (Fujita et al. 2009; Aoubala et al. 2011), *Bcl-2* (Aoubala et al. 2011), and *mir-34a* (Fujita et al. 2009). Similar observations were made for Δ122p53 (Slatter et al. 2011).

Δ122p53 promotes invasion and metastasis

Tumors in Δ122p53 mice are highly likely to metastasize (Slatter et al. 2011; Roth et al. 2016). Sarcomas in mice with at least one Δ122p53 allele metastasize to multiple sites, which is seldom found with sarcomas from p53-null mice (Roth et al. 2016). This is similar to mice heterozygous for the human R273H mutant (R270H in mouse, $p53^{R270H/+}$), a model of a LFS mutation (Olive et al. 2004). Although these mice had similar survival curves to $p53^{+/-}$ mice they showed an increased tumor burden, a different tumor spectrum, and an increased number of metastases compared to $p53^{+/-}$ mice (Olive et al. 2004). Thus, Δ122p53 may have gain-of-function (GOF) properties similar to human p53 tumor mutants [reviewed in (Lozano 2010; Garcia and Attardi 2014)]. Consistent with Δ122p53 promoting invasion and metastasis, scratch-wound and Transwell assays showed that mouse embryo fibroblasts (MEFs) from Δ122p53 mice had increased migratory capacity compared to MEFs from p53-null mice (Roth et al. 2016), and when one WT p53 allele was present (i.e., from $p53^{+/\Delta122p53}$ mice), the migratory capacity was further enhanced. Again, this suggests that WT p53 and Δ122p53 can cooperate in some contexts. Migration in these assays was reduced with neutralizing antibodies to the cytokine Interleukin (IL)-6 and C–C motif chemokine ligand 2 (CCL2) secreted by Δ122p53 MEFs (Roth et al. 2016), and was associated with changes in the polarity of actin fibers, similar to those observed with GOF p53 mutants (Muller et al. 2011). In addition, Δ122p53 increased the proportion of cells able to invade through a collagen matrix suggesting Δ122p53 can remodel the ECM (Roth et al. 2016; Campbell et al. 2018), a process commonly seen in invasive and metastatic tumors. This was also demonstrated with the Δ133p53 α, β, and γ isoforms (Campbell et al. 2018). The invasion process required activity of the Janus Kinase (JAK) and signal transducer and activator of transcription (STAT) pathway, as well as RhoA–ROCK activity, as migration was blocked with inhibitors of these enzymes (Campbell et al. 2018). Finally, mice receiving B16 melanoma cells transduced with Δ122p53 developed lung colonies metastases

earlier than controls, which were larger and more invasive (Roth et al. 2016).

Sarcomas from Δ122p53 mice showed elevated expression of α-enolase on the cell surface, a glycolytic enzyme known to promote invasion of transformed cells by ECM degradation (Sawhney et al. 2015). Increased migration of hematopoietic cells by α-enolase may also explain the multiple lymphocyte aggregates found in the lungs and livers of Δ122p53 mice (Slatter et al. 2011; Sawhney et al. 2015) (see below).

In other studies, breast cancer cells showed upregulation of Δ133p53β isoform, which was coupled with cancer stem cell (CSC) potential, increased expression of cell pluripotency/reprogramming factors including OCT3/4, NANOG, and SOX2, thus having higher metastatic potential and chemoresistance (Arsic et al. 2015). Also, the glioblastoma cell line, U87, depleted for Δ133p53α isoform was unable to promote endothelial cell migration and tubulogenesis in vitro and tumor angiogenesis in vivo (Bernard et al. 2013).

In contrast to the pro-oncogenic features of Δ122p53 (and Δ133p53), Δ122p53 displays some tumor suppressor properties. When Δ122p53 mice were crossed with a hypomorphic p53 mutant mouse (mΔpro), to generate $p53^{\Delta 122p53/mΔpro}$ heterozygotes, the mice survived better, with a median survival of 275 days compared to 144 and 149 days for p53-null mice and $p53^{mΔpro/-}$ mice (Slatter et al. 2011, 2015). These mice also showed increased mΔpro protein stabilization and enhanced cell cycle arrest in response to DNA damage (Slatter et al. 2015). Thus, the isoform may cooperate with p53 in some circumstances. This has also been suggested for ZΔ113p53, which enhanced the ability of Zp53 to activate *p21* and *mdm2* (Chen et al. 2009).

Δ122p53 promotes inflammation

Inflammation contributes to cancer (Hanahan and Weinberg 2011). Patients with inflammatory conditions including Barrett's esophagitis, ulcerative colitis and Crohn's disease have an increased risk of cancer (Tamura and Schulman 1971; Terzić et al. 2010). Ample evidence shows that dysregulation of the p53 tumor suppressor pathway contributes to increased inflammation and autoimmunity [reviewed in (Munoz-Fontela et al. 2016)]. WT p53 inhibits STAT1, the transcription factor required to transactivate interferon (IFN)-inducible genes and pro-inflammatory cytokines [reviewed in (Cheon et al. 2014)] and genes regulated by nuclear factor kappa B (NF-κB) (Gudkov et al. 2011). Δ122p53 mice showed unique pathologies that resemble those associated with chronic inflammation and autoimmunity (Slatter et al. 2011; Campbell et al. 2012), and which generally preceded tumor development. The presence of the Δ122p53 allele was commonly associated with vasculitis, a condition often seen in the patients with autoimmune rheumatic diseases such as systemic lupus erythematosus (SLE) (Cieslik et al. 2008) and rheumatoid arthritis (RA) (Bartels and Bridges 2010), as well as hepatitis and skin ulcers (Slatter et al. 2011). In addition, the Δ122p53 mice showed a high frequency of non-malignant lymphocyte aggregations in multiple organs, extramedullary haematopoiesis and prominent Peyer's patches (Slatter et al. 2011; Campbell et al. 2012). The serum of Δ122p53 mice also showed increased concentrations of pro-inflammatory cytokines (Machado-Silva et al. 2010; Slatter et al. 2011) including IL-6, IFN-γ, TNF-α, granulocyte-macrophage colony-stimulating factor (GM-CSF) and CCL2. A more extensive list of cytokines in Δ122p53 mice is in Table 1. Of these, IL-6 was found to be 12-fold higher in the serum of the Δ122p53 mice compared to the WT p53 mice. IL-6 is a pro-inflammatory cytokine that mediates its functions by activating JAK and recruiting STAT-3 to induce transcription of genes involved in inflammation (Fig. 3b). This observation was further supported by microarray analysis of splenocytes from Δ122p53 mice, which showed enrichment for pro-inflammatory transcripts including the JAK–STAT and IFN pathways (Slatter et al. 2011; Campbell et al. 2012).

The importance of inflammatory signaling in the tumor phenotypes of Δ122p53 mice was further demonstrated withΔ122p53 mice that lacked the IL-6 gene. Δ122p53/IL6-null mice showed reduced levels of multiple serum cytokines and chemokines that are part of the JAK–STAT signaling pathway, as well as a reduction in tumor incidence and metastasis (Campbell et al. 2018). In addition, PBMC from Δ122p53 mice had high levels of TNF-α after plasminogen activation, which was abrogated upon NF-κB inhibition (Sawhney et al. 2015). This is consistent with findings in human cells where increased NF-κB activity and expression of NF-κB target genes, including IL-6, occurred in gastric carcinoma cell lines transfected with a Δ133p53*α* expression plasmid (Wei et al. 2012). And, induction of NF-κB signaling in response to *H. pylori* infection required expression of both Δ133p53α and WT p53 (Wei et al. 2012). Of note however, Δ133p53α was found to reduce the levels of IL-6 in CD8+/CD28- T cells suggesting some tissue specificity in the way the isoforms function (Turnquist et al. 2016).

Δ122p53 mice have an autoimmune phenotype

Alpha enolase auto-antibodies are frequently detected in systemic autoimmune disorders and in some cases these are associated with severe endothelial damage (Pratesi et al. 2000). Although auto-antibodies to α-enolase were not investigated, Δ122p53 mice did show increased levels of other auto-antibodies (Campbell et al. 2012). These included nuclear antigens, proliferating cell nuclear antigen (PCNA), SSA, SSB, and Sm/RNPs (Campbell et al. 2012). Increased PCNA auto-antibodies are found in SLE patients, and SSA

Table 1 Cytokines and chemokines altered in the Δ122p53 model

Cytokine/chemokine	Change in Δ122p53[a]	Cytokine function	Role in cancer	References
GM-CSF	Increased	Hematopoietic growth factor and immune modulator	Involved in the recruitment of circulating neutrophils, monocytes, and lymphocytes into the tumor microenvironment	Shi et al. (2006), Francisco-Cruz et al. (2014)
IFN-γ	Increased	Important activator of macrophages and MHC-II expression	Mostly thought to be involved in anti-tumor immunity. However, recent evidence suggests pro-tumorigenic functions in certain environments	Zaidi and Merlino (2011), Kursunel and Esendagli (2016)
IL3	Increased	Bridges innate and adaptive immunity. Stimulates myeloid progenitor cell differentiation and proliferation	Overexpression of IL3 has been associated with oncogenesis and correlated with reduced patient survival in those with AML	Broughton et al. (2012), Broughton et al. (2014)
IL5	Increased	Stimulates B-cell growth and secretion of immunoglobulin	Innate IL5 producing cells increased in response to invasion and suppresses metastasis through eosinophil regulation in lung cancer Shown to increase migration and invasion in bladder cancer	Simson et al. (2007), Ikutani et al. (2012), Lee et al. (2013)
IL-6	Increased	IL-6 is an important factor in cell migration, especially monocytes. Involved in the differentiation of activated B cells	Has been shown to promote invasion, angiogenesis, and metastasis in a variety of cancers	Dankbar et al. (2000), Wei et al. (2003), Huang et al. (2004), Ancrile et al. (2007), Ara and Declerck (2010), Lederle et al. (2011), Yadav et al. (2011)
TNF-α	Increased	Primary role, regulation of immune cells including macrophages	Involved in tumor invasion through the induction of MMPs, angiogenesis through the induction of IL8, and migration and metastasis through NF-κB	Nabors et al. (2003), Hagemann et al. (2004), Cheng et al. (2007), Wang and Lin (2008), Parameswaran and Patial (2010)
Rantes (CCL5)	Decreased	Chemoattractant for blood monocytes, memory T-helper cells, eosinophils, and basophils	Act as growth factors, promote tumor angiogenesis, facilitate recruitment of stromal and inflammatory cells, and plays role in immune evasion mechanisms	Wang et al. (2015), Aldinucci and Colombatti (2014)

[a]Compared to WT and p53 null mice. *AML* acute myeloid leukemia, *MMP* matrix metalloproteinase

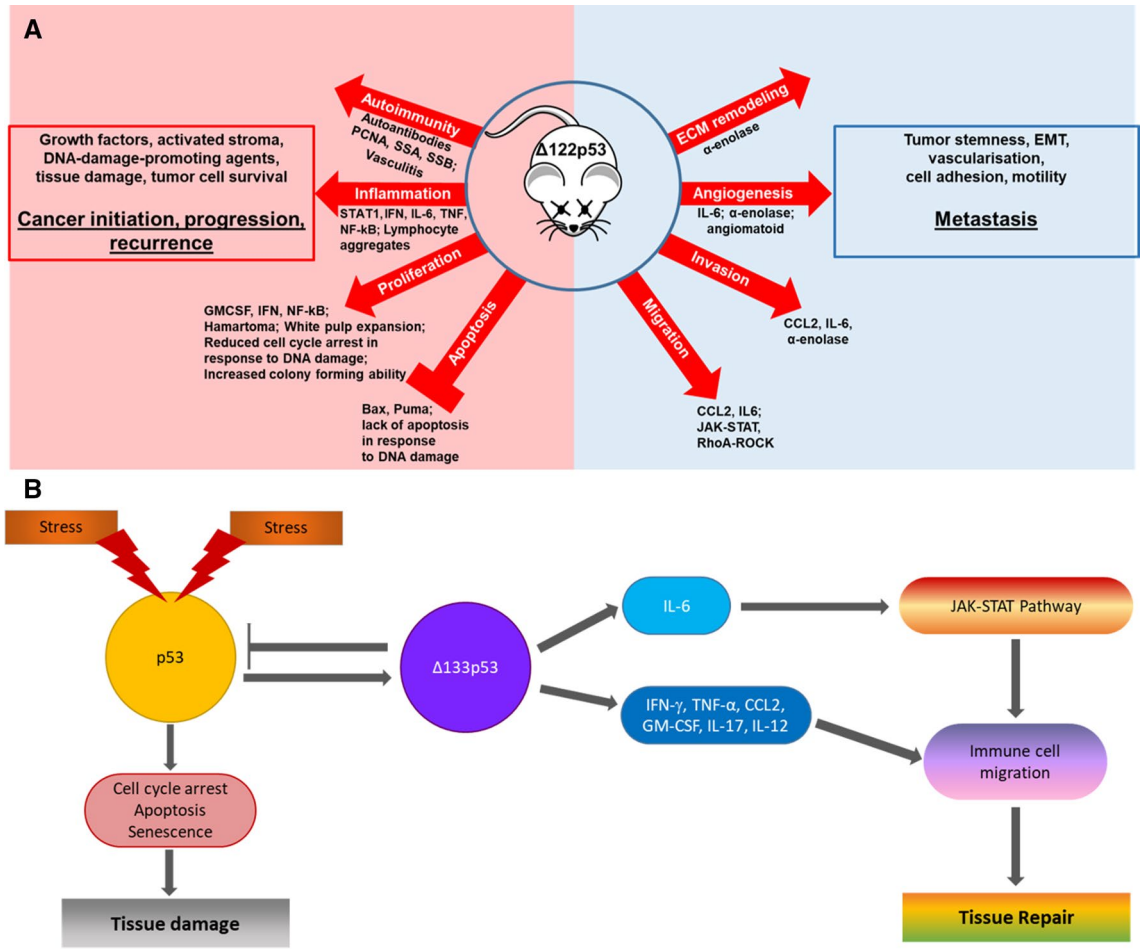

Fig. 3 Overview and model of the tumor-promoting properties of Δ133p53 derived from the Δ122p53 mouse. **a** *Bax* proapoptoic BCL2-associated X protein, *Bbc3*/*Puma* BCL2 binding component 3, *CCL2* C–C motif chemokine ligand 2, *GM-CSF* colony-stimulating factor, *IFN* interferon, *IL*-6 interleukin 6, *NF-κB* nuclear factor kappa B, *PCNA* proliferating cell nuclear antigen, *RhoA–ROCK* ras homolog family member A-Rho-associated protein kinase, *STAT* 1 signal transducer and activator of transcription 1, *JAK–STAT* Janus tyrosine kinase-STAT, *TNF* tumor necrosis factor alpha. **b** Cellular stress activates WT p53 causing the cells to either arrest cell cycle, undergo apoptosis or senescence leading to tissue damage, while on the other hand it also increases the expression of the Δ133p53 isoform. This in turn leads to elevation of expression of IL-6 and other cytokines which activate the JAK–STAT pathway facilitating immune cell migration to enable tissue repair. The Δ133p53 isoform also negatively regulates the expression of WT p53 to create a negative feedback loop

and SSB are found in Sjogren's syndrome and subtypes of SLE, including those with vasculitis (Castro and Gourley 2010; Kaneda et al. 2004).

Role of the Δ133p53 isoform in human cancers

The studies outlined above suggest that the Δ133p53 isoforms play an important role in tumor progression by promoting invasion and metastasis. In support of this, elevated expression of Δ133p53 isoforms has been reported in breast cancer (Bourdon et al. 2005; Gadea et al. 2016), colorectal cancer (Arsic et al. 2017; Campbell et al. 2018; Gadea et al. 2016), lung cancer (Fragou et al. 2017) and others, and are often associated with more aggressive tumors and poor prognosis (Arsic et al. 2017; Campbell et al. 2018; Gadea et al. 2016; Nutthasirikul et al. 2013) (Table 2). Additionally, studies in human cell lines have shown pro-tumorigenic functions of Δ133p53 that have been attributed to negative regulation of apoptosis (Bourdon et al. 2005; Arsic et al. 2017), cell cycle progression (Aoubala et al. 2011), replicative senescence (Fujita et al. 2009), angiogenesis (Bernard et al. 2013), and by promoting cell stemness, EMT, migration/invasion (Campbell et al. 2018; Arsic et al. 2015; Gadea et al. 2016; Xie et al. 2017) (Table 2). Thus, unlike WT p53, Δ133p53 appears to function as an oncogene. Furthermore, given that inflammatory cytokines are important in

Table 2 Δ133p53 isoform associations from clinical cancer-related studies and cell lines

Type of research	Type of cancer/cell type	3′	Associations with isoform	References
Clinical	Bile duct	–	Shorter survival in patients	Nutthasirikul et al. (2013)
	Breast	β	Metastatic dissemination and patients' death	Gadea et al. (2016)
		α	Present in the majority of tumors	Bourdon et al. (2005)
	Colorectal	β	High risk of metastatic recurrence	Arsic et al. (2017), Campbell et al. (2018), Gadea et al. (2016)
		–	Increased in cancer compared to normal adjacent tissue with WT p53	Fujita et al. (2009)
	Gastric	–	Increased in cancer compared to normal adjacent tissue	Ji et al. (2015)
	Lung	–	Increased in cancer compared to normal adjacent tissue	Fragou et al. (2017)
	Ovarian	–	Improved recurrence free survival with mutant p53	Hofstetter et al. (2010)
	Renal	β	Detected in tumor but not normal adjacent tissue Tumor	Song et al. (2009)
Cell line/cells	H1299 (co-transfection wt p53 and Δ133p53)	α	Inhibition of WT p53-mediated apoptosis	Bourdon et al. (2005)
	HCT116, SW480, SW620	β	Suppression of RhoB -induced apoptosis	Arsic et al. (2017)
	H1299, U2OS, HCT116, MCF-7, NHDF	α	Regulation of cell cycle arrest and apoptosis	Aoubala et al. (2011)
	MCF-7, C3LND and D3H2LN	β	Promote cancer stem cell potential	Arsic et al. (2015)
	MRC-5, WI-38	α	Regulation of replicative senescence	Fujita et al. (2009)
	U87, U2OS	α, γ	Promote angiogenesis	Bernard et al. (2013)
	AGS and SNU-1	α	Immune response	Wei et al. (2012)
	HCT116, MDA-MB231, MDA-MB231 D3H2LN, MCF-7, LoVo, SW480, SW620, Colo205	β	Enhance migration and invasion and promote EMT	Gadea et al. (2016)
	HCT116	α, β, γ	Promote RhoA-dependent invasion	Campbell et al. (2018)
	HCT116	β	Promote ROCK-driven actin reorganization	Campbell et al. (2018)
	H1299 (with Δ133p53), A549	α	Reduces mitochondria DNA repair by WT p53	Liu et al.(2017)
	Primary fibroblasts, astrocytes, and pluripotent stem cells	α	Reduced senescence and SASP phenotype	Turnquist et al. (2016), von Muhlinen et al. (2018), Horikawa et al. (2017)
	Primary T cells	α	Rescues aging and tumor-associated immune cell decline	Mondal et al. (2013)
	Primary HASMC	α	Increased migration and proliferation	Xie et al. (2017)

H1299—lung p53-null; HCT116, SW480, SW620—colon; MCF-7, MDA-MB231, C3LND, D3H2LN—breast; U2OS—osteosarcoma; U87—glioblastoma; AGS, SNU-1—gastric; MRC-5, WI-38, *NHDF* normal human fibroblast strains; "–" not attributed to individual Δ133p53 isoforms; *SASP* senescence-associated secretory phenotype, *HASMC* human artery smooth muscle cell

mediating the phenotypes of Δ122p53, we would predict that tumors with high Δ133p53 expression would show evidence of immune cell infitration.

Finally, in addition to the anti-apoptotic function reported for ZΔ113p53, it was also found to promote multiple DNA double-strand breaks (DSB) repair (Chen et al. 2005, 2009; Gong et al. 2015) pathways. This included single strand repair, homologous recombination, and non-homologous end-joining and this was associated with increased expression of *RAD51, RAD52*, and *LIG4* mRNA. This report also showed that Δ133p53α could carry out similar functions. Thus, when elevated in cancers, Δ133p53 isoforms might reduce the effectiveness of radiotherapy and chemotherapy.

Summary and conclusions

Overall, studies using the Δ122p53 mouse as a model of Δ133p53 have shown that all Δ133p53 family members have oncogenic capability. Δ122p53 is multi-functional

(Fig. 3a), conferring survival and proliferative advantages on cells and promoting invasion, metastasis, and vascularization. These processes are specific to the isoforms, and are not due to dominant negative activity on p53, although they are capable of overriding p53 in some contexts. Moreover, Δ122p53 may even cooperate with p53. Consistent with the above properties, cancers with high levels of Δ133p53 have poor outcome. A key feature of Δ122p53 is that it mediates its effects through the JAK–STAT signaling pathway, leading to increased NF-κB activity and increased pro-inflammatory cytokine levels (importantly IL-6), as well as increased RhoA–ROCK signaling, to promote (cancer) cell migration (Fig. 3B). Thus, patients whose cancers have elevated Δ133p53 expression may benefit from drugs targeting the above pathways.

In conclusion, we suggest that the Δ133p53 isoforms have evolved as pro-inflammatory signaling molecules, 'designed' perhaps to deal with the consequences of p53 activation. When p53 is activated by DNA damage, virus infection, or other stressors, tissue damage results. Thus, p53 induces Δ133p53 to promote a transient inflammatory response to manage the damage. As Δ133p53 increases, it will lower p53 activity in a negative feedback loop (Fig. 3b). However, if Δ133p53 expression becomes sustained by some mechanism, chronic inflammation ensues, eventually resulting in various pathologies including malignancy.

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Compliance with ethical standards

Conflict of interest The authors declare no potential conflicts of interest.

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