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Tissue-specific expression of p73 C-terminal isoforms in mice

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Abbreviations: TA, TAp73; ΔN, ΔNp73; SAM, sterile alfa motif; eto, etoposide; cispl, cisplatin; untr, untreated; FWD, forward; REV, reverse; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; PBS, phosphate buffered saline; PARP, poly (ADP-ribose) polymerase; ORF, open reading frame; AEC, ankyloblepharon-ectodermal dysplasia-clefting; SHFM, split-hand-foot malformation

p73 is a p53 family transcription factor. Due to the presence in the 5' flanking region of two promoters, there are two N-terminal variants, TAp73, which retains a fully active transactivation domain (TA), and ΔNp73, in which the N terminus is truncated. In addition, extensive 3' splicing gives rise to at least seven distinctive isoforms; TAp73-selective knockout highlights its role as a regulator of cell death, senescence and tumor suppressor. ΔNp73-selective knockout, on the other hand, highlights anti-apoptotic function of ΔNp73 and its involvement in DNA damage response. In this work, we investigated the expression pattern of murine p73 C-terminal isoforms. By using a RT-PCR approach, we were able to detect mRNAs of all the C-terminal isoforms described in humans. We characterized their in vivo expression profile in mouse organs and in different mouse developmental stages. Finally, we investigated p73 C-terminal expression profile following DNA damage, ex vivo after primary cultures treatment and in vivo after systemic administration of cytotoxic compounds. Overall, our study first elucidates spatio-temporal expression of mouse p73 isoforms and provides novel insights on their expression-switch under triggered conditions.

Introduction

p73 is a p53-related transcription factor with fundamental roles in development,[1-4] tumor suppression[5-11] and senescence.[12-23] Transcription from two different promoters on the *TRp73* gene results in generation of TAp73 and ΔNp73 isoforms with opposing pro- and anti-apoptotic functions.[24-28] Although p73 shares tumor-suppression functions with p53,[29-44] it plays some very distinctive roles in development.[45-47] Mice lacking p73 show neurodegeneration, defects in pheromone detection as well as chronic infection and inflammation that lead to a shorter lifespan.[3] In vivo studies demonstrated that more than 70% of mice lacking TAp73 develop tumors.[48] On the other hand, ΔNp73 isoforms are known to exhibit dominant-negative activity toward the tumor-suppressor functions of both TAp73 and p53 and also act as a negative regulator of DNA damage response.[27,49-53] Besides, ΔNp73 interferes with many developmental programs, such as the myogenic differentiation program.[54] Moreover, both TAp73 and ΔNp73 KO models show mild degenerative phenotypes, underlying the importance of p73 in brain development.[48,55-60]

This scenario becomes even more complex by focusing on the C terminus, where many splicing events occur, giving rise to at least seven different isoforms.[61] p73α is the only one that contains a fully functional sterile alpha motif (SAM), which has been described as a putative protein-protein interaction domain.[62-64] TAp73γ rises from alternative splicing at exon 11 and p73δ, missing exon 11, 12 and 13.[65] Although p73γ retains all the exons coding for SAM domain, the splicing event at exon 11 produces a shift of the reading frame, leading to a premature STOP codon.[65] Stimulation of human peripheral blood led to identification of two additional isoforms, p73ε and p73ζ, with p73ε lacking exon 11 and 13 and p73ζ excluding exons 11 and 12.[66] Elucidation of p73ζ isoform clarifies that this splicing variant includes most of the SAM domain, although it misses a hydrophobic residue that seems to be fundamental for stability and consequent domain functionality.[66] Similar observation was pointed out in this study, regarding the isoform p73ε. In this case, the deletion covers the first three amino acids of an α-helix, negatively influencing proper folding of the domain. Even if p73γ encodes for all the exons involved in the SAM domain, due

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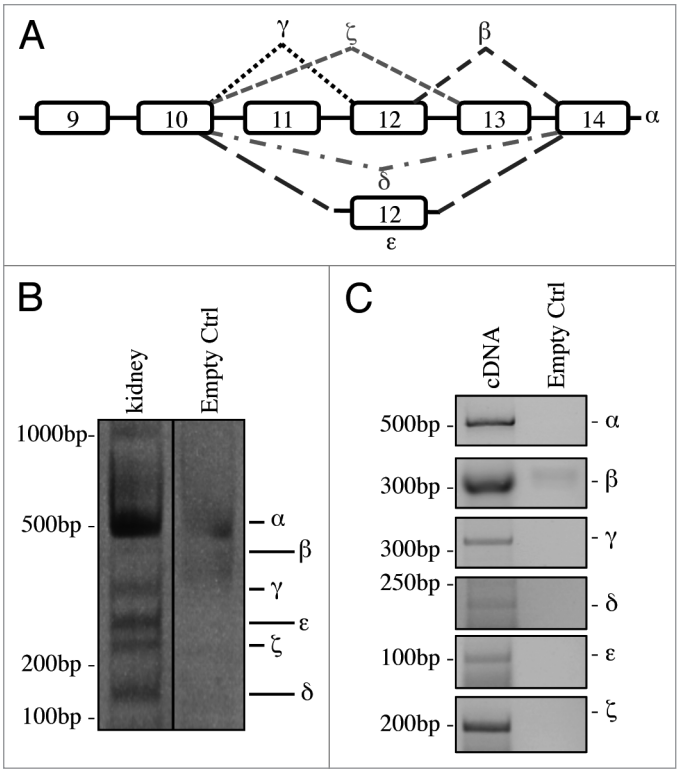

Figure 1. C-terminal isoforms of p73. (**A**) Schematic representation of splicing of human C-terminal p73. (**B**) RNA from kidney of adult mouse was reversed transcribed and cDNA was amplified by PCR. Product was run on 10% acrylamide gel. All the isoforms identified in human were detected and distinguished for different nucleotide length. (**C**) cDNA derived from an adult mouse was also amplified using isoforms-specific primers for each specific splicing variants. PCR products were run on agarose gel. All experiments have been repeated at least three times. Ctrl, control (DNase RNase-free H_2O).

to the splicing at exon 11, the open reading frame is different.[65,67] Here, we investigated the tissue spatiotemporal expression profile of all p73 isoforms in mice and their expression switch under stressed conditions.

Results

Identification of mouse p73 C-terminal isoforms. **Figure 1A** reports a schematic representation of the alternative splicing occurring in the C-terminal region of human p73 gene. Based on this, we tried to understand whether all the isoforms identified in human were also present in the mouse. There are commercial antibodies available, sensitive enough to detect p73 and its N-terminal variants;[68,69] however, these antibodies fail to discriminate C-terminal isoforms at endogenous levels in the mouse. For this reason, we monitored mRNA levels. Organs from adult (2-mo-old) C57Bl/6 mice were collected and RNA was extracted. cDNA derived from kidney was then used for PCR in saturating conditions (40 cycles). PCR was performed by using forward and reverse primers designed, respectively, on exons 10 and 14. As an empty control we used RNase DNase-free water. We were able to detect all the isoforms, although the signal deriving from some of them was much weaker than others (**Fig. 1B**). To overcome this problem and to further prove the existence of all isoforms, we performed a PCR using isoform-specific primers designed at the specific exon-exon junctions. Through this strategy, we generated a specific PCR for each C-terminal splicing variant. As shown in **Figure 1C**, all the isoforms were easily detected. Identity of the isoforms was further confirmed by DNA sequencing on PCR products.

Analysis of organ-specific expression of mouse p73 C-terminal isoforms. The expression of human p73 variants has been characterized in different tissues and cell lines.[65,66,70,71] Since the expression pattern in the mouse has still not been investigated, we analyzed different organs using the same strategy used in **Figure 1B** and performing PCR in saturating conditions (40 cycles) in order to detect all possible isoforms. We found out that C-terminal variants of p73 are expressed in all the organs tested, even if at different levels, with p73α being the most abundant (**Fig. 2**). Since we detected also products at unexpected mobility shifts, we sequenced all of them, but we failed to identify brand new isoforms, while we confirmed presence of all the variants previously described in human.

Analysis of isoforms expression at different developmental stages. We then focused on expression upon different developmental stages, since p73 seems to be a key regulator in this process.[60,72-75] We started from embryonic up to adult stages (2-mo-old). In this case, we performed a semi-quantitative RT-PCR (30 cycles). Quantification was done in relationship with starting levels (E12). Also in this system, p73α was the most abundant isoform, even if it did not undergo major changes, while p73ζ, but also to a smaller extent, p73ε and p73δ, were upregulated over time (**Fig. 3A and B**). p73γ, on the other hand, was downregulated during development (**Fig. 3A and B**). We also monitored levels of TAp73 (25 cycles) and ΔNp73 (30 cycles); we determined that TAp73 was more abundant than ΔNp73, even if, on the other hand, there was no significant regulation during development of any of the N-terminal variants (**Fig. 3A and C**). This type of analysis also revealed other migrating bands at unexpected sizes (**Fig. 3A**), which were sequenced, but revealed to be not specific.

Analysis of isoforms expression upon DNA damage in vitro. Since p73 is induced upon DNA damage and its loss confers resistance to cell death,[48,76-78] we checked whether cytotoxic drug treatments, with cisplatin[79,80] or etoposide,[81-84] affected expression levels of C-terminal isoforms in the N2a cell line. In semi-quantitative RT-PCR, α-isoform results slightly increased, while p73β and p73ζ appeared strongly decreased (**Fig. 4A–C**). In another system instead, the expression levels of the isoforms varied slightly. Indeed, in spleen-derived primary splenocytes, p73γ and p73ε were the two most upregulated isoforms upon DNA damage, while p73ζ was downregulated, consistently with the results in N2a cells (**Fig. 5A and B**). In this scenario, we also monitored levels of N-terminal isoforms. TA levels at 24 h were lower than untreated cells, while ΔN levels were comparable between treated vs. untreated at 24 h. Levels of TA and ΔN were lower at 24 h than at 6 h, probably due to ongoing massive apoptotic events, as demonstrated by PARP cleavage[85-89] (**Fig. S1**).

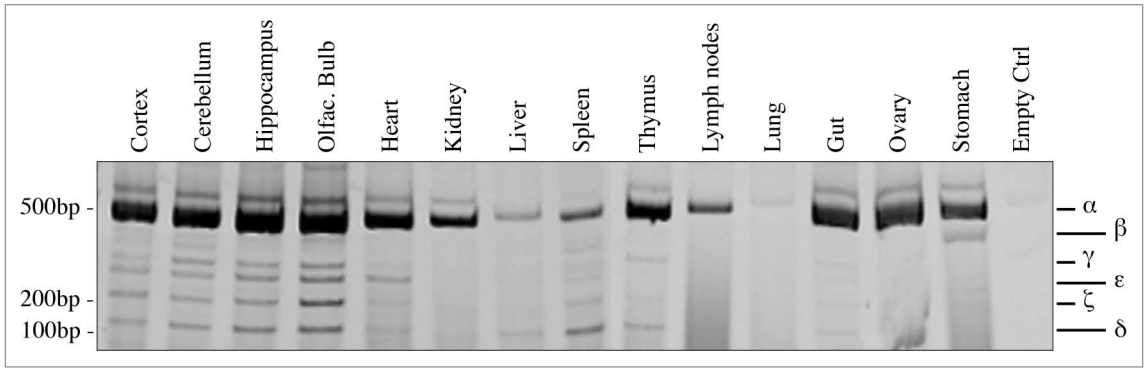

Figure 2. Organs-specific expression of p73 C-terminal isoforms. Screening of the isoform expression in organs of 2-mo-old mice. RT-PCR was performed using primers that amplify all isoforms (exons 10–14, mp73-X10 FWD and mp73-X14 REV). Samples were analyzed as in **Figure 1B,** and representative result is depicted. Experiments have been reproduced at least three times. Olfac. Bulb, olfactory bulb; ctrl, control.

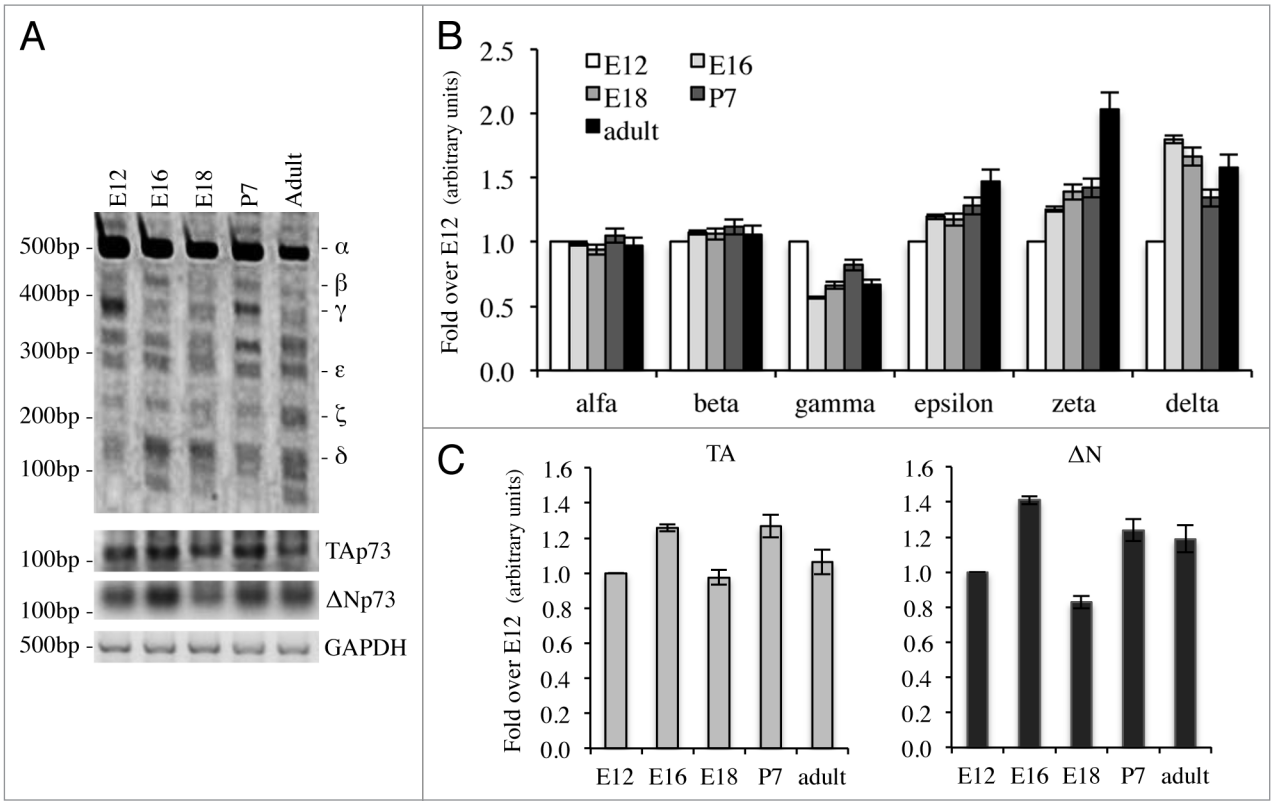

Figure 3. Expression of C-terminal isoforms during mouse development. Screening of the isoform expression during mouse development starting from embryonic stage E12, reaching adult (2 mo) age. Samples were analyzed as in **Figure 1B** and a representative result is depicted in (**A**). Semi-quantitative RT-PCR (30 cycles for C-terminal p73, 20 cycles for GAPDH) was performed and samples were run on a 10% acrylamide gel. Densitometry analysis was performed on at least three gels in order to quantify C-terminal isoforms levels (**B**) or TAp73 and ΔNp73 levels (**C**). Experiments have been repeated at least three times. E, embryonic stage; P7, seventh day after birth; TA, TAp73; ΔN, ΔNp73; GAPDH, glyceraldehyde 3-phosphate dehydrogenase.

Analysis of isoforms expression upon DNA damage in vivo. Finally, we investigated the effects on levels of p73 C-terminal isoforms in vivo upon DNA damage. We treated adult mice intra-peritoneally and analyzed levels of C-terminal isoforms 20 h after treatment. We had different outcomes in relationship to the tissue analyzed, probably due to the ability of the drug to reach different organs but most likely also depending on starting endogenous levels of p73. In some organs, such as in the lung, all the isoforms were induced (**Fig. 6A–C**), while in other organs, there were no detectable effects of p73 levels, such as in the heart (data not shown). Moreover, in other tissues there were varying effects depending on the treatment that the animal received; in the spleen for example, etoposide was capable of inducing all isoforms (**Fig. 6D and E**), while cisplatin was causing a shift from α-isoform toward p73γ and p73δ (**Fig. 6D and F**).

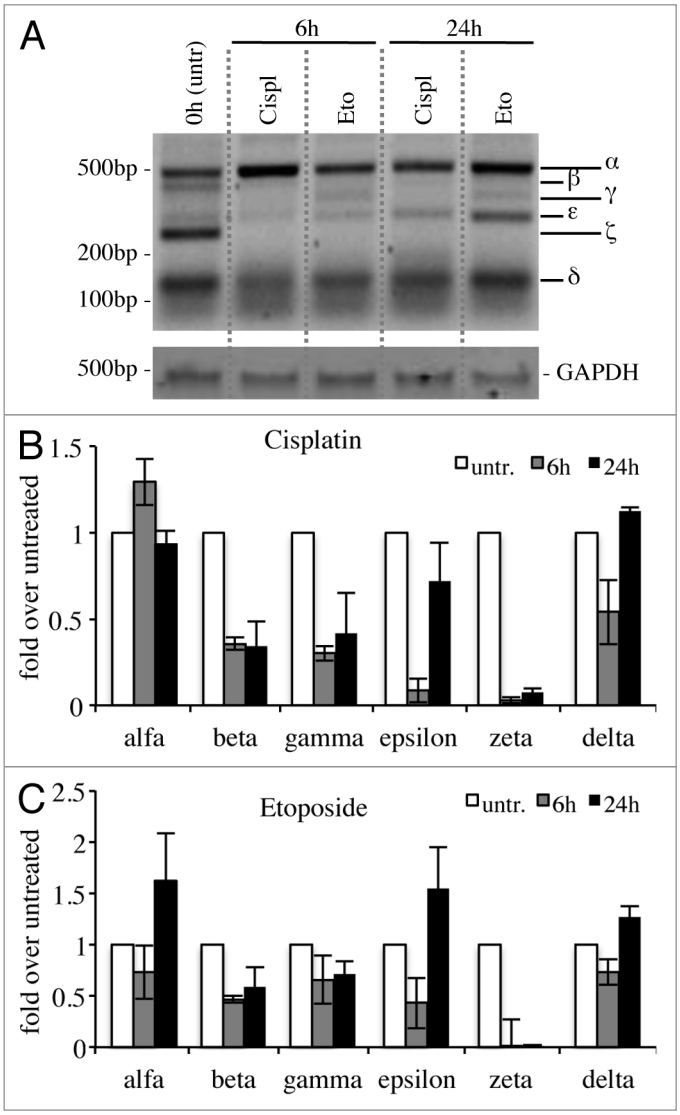

Figure 4. C-terminal isoform expression upon DNA damage in vitro. N2a (neuroblastoma cell line) were treated with 1 μg/ml etoposide or 5 μg/ml cisplatin, collected at the indicated time points and processed. Semi-quantitative RT-PCR (30 cycles for C-terminal p73, 20 cycles for GAPDH) was performed, and samples were run on a 10% acrylamide gel. A representative example (of at least three experiments) is depicted in (**A**). Densitometry analysis of at least three gels was achieved, relative to untreated cells, upon cisplatin treatment (**B**) or etoposide treatment (**C**). Cispl, cisplatin; Eto, etoposide; untr., untreated; GAPDH, glyceraldehyde 3-phosphate dehydrogenase.

Discussion

Here, we identified and characterized the tissue-specific expression of C-terminal isoforms of murine p73. This has been partly published regarding human p73, while investigation on its murine counterpart has been totally neglected. The isoform-specific KO mice models focused only on the characterization of p73 N terminus.[48,55,56] These tools yield a lot of insight into understanding functions and roles of the specific N-terminal isoforms of p73; however, they leave some unsolved questions, since not all the defects displayed by the full $p73^{-/-}$ mouse[3] were represented in one of these two models. For example, both $TAp73^{-/-}$ and $\Delta Np73^{-/-}$ show mild neurological defects, while the full $p73^{-/-}$ displays a more penetrant phenotype; besides, the strong immunological defect found in the full $p73^{-/-}$ mice is absent in the $TAp73^{-/-}$ or $\Delta Np73^{-/-}$, leading to the conclusion that other factors might be involved. We may speculate that TAp73 and ΔNp73 could have overlapping functions that allow one isoform to overcome the absence of the other and vice versa. Moreover, C-terminal domains might play a role in this, since in the N-terminal KO models they were still expressed and functional in the remaining N-terminal isoform. As support to this theory, there is the presence of a sterile alpha motif (SAM) at the C terminus of p73. SAM domains are small putative protein-protein interaction domains,[90] and in the mouse, this region overlaps exons 12–14 of p73;[63] therefore, only α encodes a fully functional SAM domain and hypothetically could have an unique pool of interaction partners. Moreover, it has been shown that p73 SAM domain, but also the extreme C terminus, are able to regulate negatively the transcriptional activity of the protein,[91,92] while on the other hand, deletion of SAM domain and extreme C terminus enhances transactivation and DNA-binding activity but inhibits apoptosis.[92] Thus, it is striking that in all the tissues analyzed, we identified α as the most abundant. It could possibly have some involvement with control of proliferation, since presence of a fully functional SAM domain apparently inhibits it. This could be an incredibly interesting and still not described aspect of control of p73. In fact, the p73β, rather than α, variant has an interesting potential to transactivate target genes.[65] This similarity retains from p63, where the C-terminal domains (TI and SAM) have been proved to act as dominant transcription repression modules.[93-99] Many mutations found in the AEC syndrome have been shown to destabilize or modify the structure of one of the helices of this region, leading to a loss of function and a consequent deregulation in transactivation and growth suppression.[100-104] These findings clearly state a connection between functionality of the SAM domain and AEC syndrome, opening possible new hints of investigation for its p73 homolog. In absence of triggers, the most preferred isoform transcribed could be p73α, due to its low transactivation potential, while upon a specific stimulus there could be a shift toward other isoforms, as we were able to highlight at developmental stages but also upon DNA damaging agents. Another interesting new aspect was highlighted by our work: no striking differences between TAp73 and ΔNp73 levels were detected during development or upon stresses. Instead C-terminal isoforms resulted to be tightly regulated; for example, during development, p73ε, p73ζ and to a lesser extent p73δ, were specifically, induced while γ was downregulated. Also, upon DNA damage in vitro and in vivo, we highlighted specific regulation of each isoform, suggesting that every C-terminal variant could play specific roles, possibly depending on the tissue or cell system analyzed. In line with this, interesting observations have been made on the C terminus of p63; in fact, mutations leading to premature stop codon in exon 14 of p63 are correlated with limb mammary syndrome and SHFM (split-hand-foot malformation).[105-107] For these reasons, a further analysis should be done in order to clarify aspects regarding p73 functions correlated with

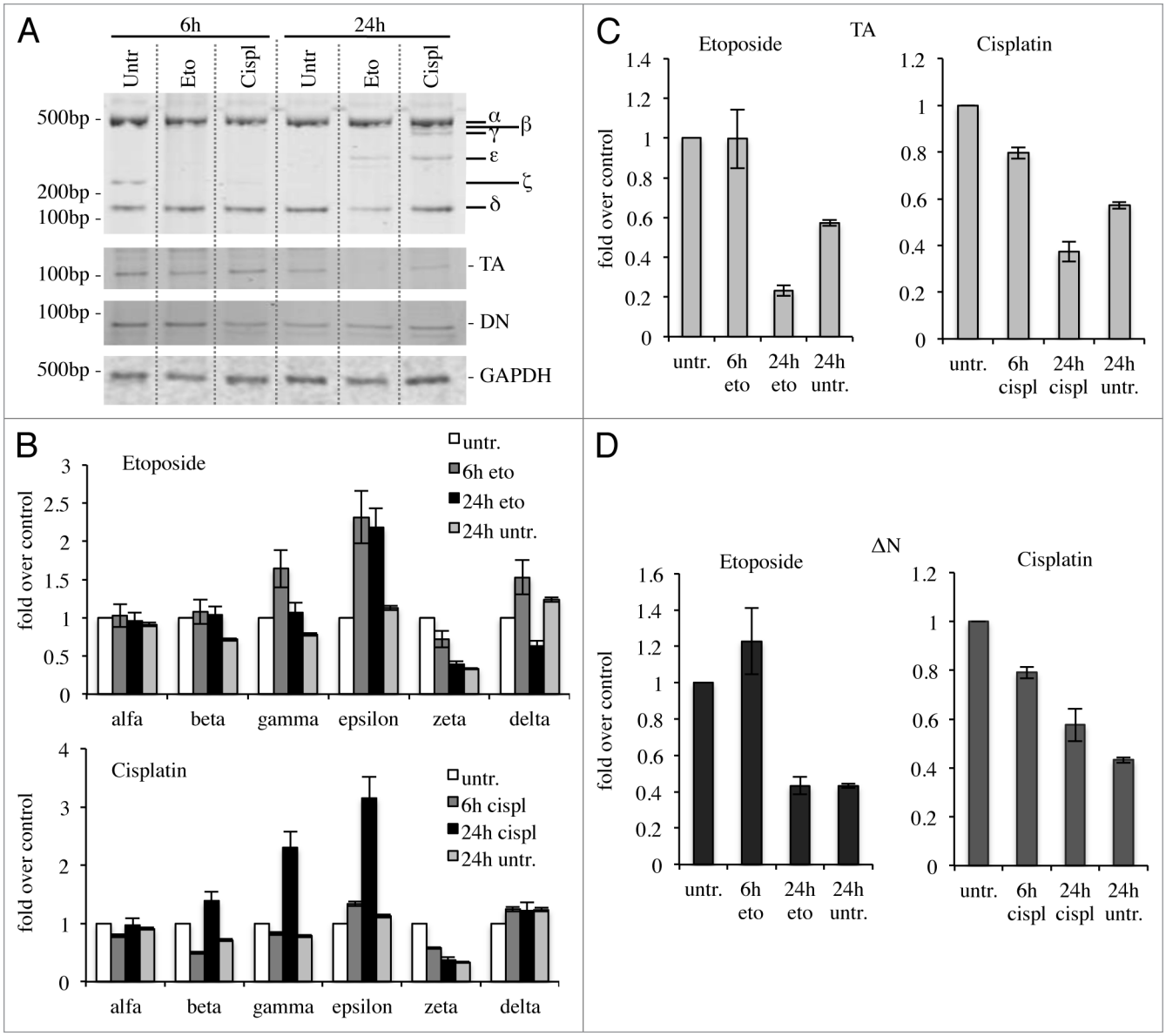

Figure 5. C-terminal isoforms expression upon DNA damage in primary splenocytes. Primary splenocytes were treated with 1 μg/ml etoposide or 5 μg/ml cisplatin, collected at the indicated time points and processed. Semi-quantitative RT-PCR (30 cycles for C-terminal p73, 20 cycles for GAPDH) was performed and samples were run on a 10% acrylamide gel. Representative result is depicted in (**A**). Densitometry analysis of at least three blots was achieved, relative to starting point (untreated, 6 h), to monitor C-terminal isoforms levels (**B**), TAp73 levels (**C**) and ΔNp73 levels (**D**) over time. Cispl, cisplatin; Eto, etoposide; untr., untreated; TA, TAp73; ΔN, ΔNp73; GAPDH, glyceraldehyde 3-phosphate dehydrogenase.

its C terminus. Moreover, it is now becoming crucial to generate C-terminal isoform-specific KO models, which could also become powerful tools for studying potential human diseases correlated by p73 misfunctions, such as neurodegeneration[108-113] and cancer.[34,114-120]

Our work also underlined the incredible necessity of developing an antibody with enough sensitivity to detect endogenous p73 C-terminal isoforms, as well as an antibody specific for the SAM domain. This would open a wide range of new directions, including screening for interaction partners, due to the putative function of the SAM. It would be intriguing to investigate influences of the SAM on tetramerization of p73, since this domain has been suggested to play a role in regulation of transcription through lipid interaction.[121-123] Studying interactions with new partners, with powerful techniques such as TAP tag[124,125] or MAPPIT,[126,127] could lead to some clarifications of p73's still unknown functions, related, for example, to strong defects in brain and chronic inflammation.

To conclude, this work identifies the C-terminal isoforms transcribed in the mouse, upon endogenous and challenging conditions. It underlines the extreme importance of studying these isoforms more in detail, since they could play a fundamental and still-not-investigated role in pathologies such as cancer, degeneration and development.

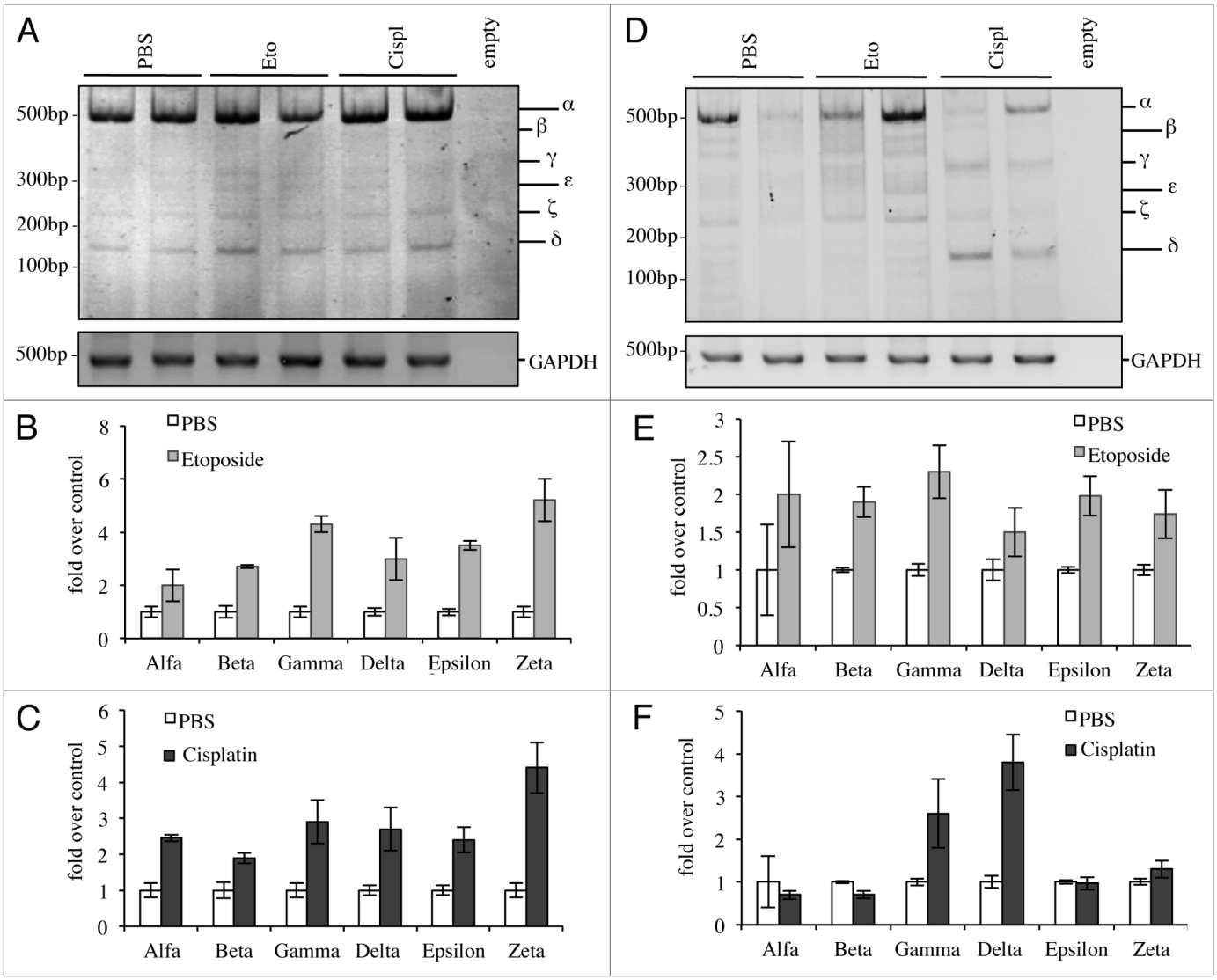

Figure 6. C-terminal isoforms expression upon DNA damage in vivo. C57Bl/6 mice (2-mo-old, n ≥ 6 per group) were treated i.p. with 10 mg/kg etoposide or 5 mg/kg cisplatin or with PBS (control group). Animals were sacrificed after 20 h and tissues were then processed. Semi-quantitative RT-PCR (24 cycles for C-terminal p73, 20 cycles for GAPDH) was performed and samples were run on a 10% acrylamide gel. Example of results deriving from lung is depicted in (**A**). Densitometry analysis of at least three blots was achieved, showing levels of C-terminal isoforms upon etoposide (**B**) or cisplatin treatment (**C**). The same was done for the spleen (**D**) and quantification upon etoposide (**E**) or cisplatin (**F**) is shown. Cispl, cisplatin; Eto, etoposide; untr., untreated; TA, TAp73; Δn, ΔNp73; GAPDH, glyceraldehyde 3-phosphate dehydrogenase.

Materials and Methods

Cells cultures, primary cells and reagents. Cells were cultured at 37°C in 5% CO_2 in culture medium. N2a were purchased from ATCC (#CCL-131) and maintained in a mix of 45% DMEM high glucose, 45% Optimem (Gibco) and 10% fetal bovine serum, 250 mM L-glutamine, 1 U/ml penicillin/streptomycin (all Gibco). Splenocytes were generated as already been described[128] and cultured in RPMI 1640 medium (Gibco), supplemented with 10% FCS, 250 mM L-glutamine, 50 mM 2-mercaptoethanol, penicillin/streptomycin (1 U/ml), non-essential amino acids and 1 mM pyruvate (all Invitrogen).

Western blotting. Western blotting was performed as previously described.[129] In brief, proteins were extracted with RIPA buffer containing cocktail inhibitors (Roche), and concentration was determined using a Bradford dye-based assay (Biorad). Total protein (30 μg) was subjected to SDS-PAGE followed by immunoblotting with appropriate antibodies at the recommended dilutions. The blots were then incubated with peroxidase-linked secondary antibodies followed by enhanced-chemiluminescent detection using Super Signal chemiluminescence kit (Thermo Scientific). Antibodies: mouse monoclonal anti PARP (1:1,000; Alexis), mouse monoclonal anti GAPDH (1:10,000; Sigma-Aldrich).

DNA damage in vivo. C57Bl/6 mice (2-mo-old) were injected i.p and sacrificed 20 h after treatment. Organs were collected and frozen on dry ice. Tissue homogenization was performed in 750 μl of TRIzol using a tissue grinder (Precellys). Mice were

bred and subjected to listed procedures under the project license released from the United Kingdom Home Office.

RNA extraction, reverse transcription and PCR analysis. RNA was extracted using TRIzol (Invitrogen) and following manufacturer's guidelines. After extraction, RNA was quantified with NanoDrop 2000 (Thermo Scientific) and 5 μg were treated with DNase I (Sigma) in order to eliminate DNA contamination. cDNA was reversed transcribed using RevertAid H Minus First Strand cDNA synthesys kit (Fermentas) and gene-specific primers (RT FWD and RT REV for C-terminal p73, GAPDH as internal control). Semi-quantitative PCR was performed using GoTaq DNA Polymerase (Promega) and the following cycle conditions: 5 min at 95°C; 30 sec at 95°C, 1 min at 58°C, 1 min at 72°C (24–40 cycles) and 10 min at 72°C; cycle number varied in relationship with the organ/cell type analyzed. PCR product was run on a 10% acrylamide gel (BioRad) and stained afterwards for 10 min in a 0.5 μg/ml ethidium bromide solution. Densitometry analysis was achieved using ImageJ software.

Primers. RT FWD 5'-GCT TGT GCC CCA GCC TTT G-3'

RT REV 5'-CCC CTC CAG ATG GTC ATA CG-3'

mp73-X10 FWD 5'-GAG ATC TTG ATG AAA GTC AAG G-3'

mp73-X10–11 FWD 5'-CAG AGG CCG AGT CAC CTG-3'

mp73-X10–12 FWD 5'-TAC AGA GGC CGC TCC GGG-3'

mp73-X10–13 FWD 5'-CAG AGG CCT TTT TTG ACA GGG-3'

mp73-X10–14 FWD 5'-CCT ACA GAG GCC GAC CTT GG-3'

mp73-X14 REV 5'-GCA TTT CCG TGT GCG CCA C-3'

mp73-X12–14 REV 5'-GCC TCG TCA GGA CCT TGG G-3'

mp73-X13–14 REV 5'-CCT GAA GCA GAG CCA TGA CTG-3'

mTAp73 FWD 5'-GCA CCT ACT TTG ACC TCC CC-3'

mTAp73 REV 5'-GCA CTG CTG AGC AAA TTG AAC-3'

mDNp73 FWD 5'-ATG CTT TAC GTC GGT GAC CC-3'

mDNp73 REV 5'-GCA CTG CTG AGC AAA TTG AAC-3'

GAPDH FWD 5'-CAA GGT CAT CCA TGA CAA CTT TG-3'

GAPDH REV 5'-GTC CAC CAC CCT GTT GCT GTA G-3'

RT FWD and RT REV along with GAPDH FWD and REV were used to reverse transcribe cDNA. Primers mp73-X10 FWD and mp73-X14 REV were used to amplify by PCR all C-terminal isoforms. Primers mp73-X10–11 FWD and mp73-X13–14 REV were used to amplify p73α specifically. Primers mp73-X10–11 FWD and mp73-X12–14 REV were used to amplify p73β specifically. Primers mp73-X10–12 FWD and mp73-X13–14 REV were used to amplify p73γ specifically. Primers mp73-X10–12 FWD and mp73-X12–14 REV were used to amplify p73ε specifically. Primers mp73-X10–13 FWD and mp73-X14 REV were used to amplify p73ζ specifically. Primers mp73-X10–14 FWD and mp73-X14 REV were used to amplify p73δ specifically.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Supplemental Materials

Supplemental materials may be found here:
www.landesbioscience.com/admin/article/22787/

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