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TAp73 transcriptionally represses BNIP3 expression

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TAp73 is a tumor suppressor transcriptional factor, belonging to p53 family. Alteration of TAp73 in tumors might lead to reduced DNA damage response, cell cycle arrest and apoptosis. Carcinogen-induced TAp73$^{-/-}$ tumors display also increased angiogenesis, associated to hyperactivition of hypoxia inducible factor signaling. Here, we show that TAp73 suppresses *BNIP3* expression, directly binding its gene promoter. *BNIP3* is a hypoxia responsive protein, involved in a variety of cellular processes, such as autophagy, mitophagy, apoptosis and necrotic-like cell death. Therefore, through different cellular process altered expression of BNIP3 may differently contribute to cancer development and progression. We found a significant upregulation of *BNIP3* in human lung cancer datasets, and we identified a direct association between BNIP3 expression and survival rate of lung cancer patients. Our data therefore provide a novel transcriptional target of TAp73, associated to its antagonistic role on HIF signaling in cancer, which might play a role in tumor suppression.

Introduction

p73 is a transcriptional factor, belonging to p53 family. The presence of 2 promoters in the TP73 gene gives rise to 2 sets of isoforms: transactivational (TA) domain-containing isoforms, TAp73, regulated by the first promoter (P1), and the N-truncated isoforms, lacking TA domain (from promoter P2), ΔNp73. Alternative splicing can also take place at 3′-end, leading to 7 isoforms varying in activity and specificity α, β, γ, δ, ε, ζ, η.[1-5] p53 family is one of the most powerful families of genes[6,7]; it plays fundamental roles in protection of genome integrity[8-13] in germline and somatic cells impacting fertility[14-21] and cancer.[22-36] In cancer cells p73 is rarely mutated, but its expression is often deregulated. There is increasing evidence, that TAp73/ΔNp73 expression ratio affects tumor development and progression.[37-39] TAp73 is considered a *bona fide* tumor suppressor, largely mimicking p53 function. It controls cell cycle arrest, apoptosis as well as DNA damage repair.[40] Tumor suppressor function of TAp73 has also been recently associated to repression of tumor angiogenesis, through regulation of hypoxia inducible factor (HIF) signaling. TAp73 indeed directly binds HIF-1a protein, promoting its oxygen-independent degradation.[41,42] Conversely, ΔNp73 antagonizes TAp73 and it is considered an oncogenic protein.[43-46] It can form inactive complexes with TAp73, and also bind common promoters with p53 and TAp73, thus inhibiting their transcriptional activity.[47-50] Besides its cancer related function, TAp73 also plays a role in neurogenesis, and its dysregulation is linked with developmental defect and neurodegenerative diseases. In fact, TAp73 is necessary for neuronal differentiation and maintenance of neuronal stem cells.[51-54]

Hypoxia inducible factors (HIFs) mediate the physiological response to hypoxia[55] regulating processes, such as angiogenesis,[56-58] proliferation[59-68] and metabolism.[64,69-73] The wide transcriptional reprogramming operated by HIF-1, includes the direct transcriptional induction of the Bcl-2 Nineteen kilodalton Interacting Protein (BNIP3).[74,75] BNIP3 is a Bcl2-family BH3-only protein, which contributes to cellular processes, such as apoptosis, autophagy, mitophagy and mitochondrial metabolism.[76] BNIP3-deficient mice do not display significant physical abnormalities and altered lifespan, however they show decreased postischemic myocardial apoptosis,[77-82] suggesting an involvement in hypoxic-dependent cell death. BNIP3 was first shown to localize in mitochondria,[83] although later in glial cells was also observed a nuclear localization.[84,85] BNIP3 activation causes mitochondrial dysfunction through mitochondrial apoptosis, reduced oxidative phosphorylation and induction of autophagy and mitophagy.[86-89]

Here, we show a direct regulation by TAp73 on BNIP3 transcription, and we report a possible clinical relevance of this axis

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for lung cancer patients. Consistently with reduced TAp73 activity, high BNIP3 expression correlates with bad prognosis in patients with lung cancer.

Results

TAp73 represses HIF1α and its target BNIP3

To investigate the influence of TAp73 on BNIP3 expression we used SaOS-2 cells with Tet-On system. SaOs-2 is a p53/p63/p73 deficient human osteosarcoma cell line. Expression of TAp73 in these cells can be induced by doxycycline treatment. As shown in **Fig. 1A, B** and **Fig. S1A**, 2 μg/ml of doxycycline induced TAp73 expression in a time-dependent manner. Along with TAp73 accumulation we detected decrease in BNIP3 protein levels and as previously described reduced HIF1α (**Fig. 1A**).[41,43] p21 was used as positive control of p73 transcriptional activation (**Fig. 1A**). To evaluate whether BNIP3 downregulation was associated to altered transcription of the *BNIP3* gene, we performed real-time qPCR in SaOs-2 Tet-On cell line. qPCR also highlighted decrease in BNIP3 mRNA level (**Fig. 1B**). Taken together these data indicate that consistently with TAp73-dependent downregulation of HIF1α BNIP3 is downregulated.

Next we employed H1299, p53-null human non-small cell lung carcinoma (NSCLC) cell line, expressing endogenous TAp73. First, we overexpressed HA-tagged TAp73 for 24 h and exposed the cells to hypoxia during the last 8h of transfection (1% O_2) (**Fig. 2A, B**). Protein and RNA levels of TAp73 and its transcriptional target p21 confirmed TAp73 transcriptional activation (**Fig. 2B**, **Fig. S1B, C**). Increased levels of BNIP3 mRNA and protein were observed in cells, under hypoxia, as *BNIP3* is a hypoxia response gene. TAp73 overexpression in normoxia and hypoxia confirmed the BNIP3 repression observed in SaOs-2 Tet-On mRNA (**Fig. 2A, B**).

Then we performed knockdown experiment in H1299 cells by transfecting selective siRNA, for TAp73 isoforms. mRNA levels of *BNIP3* resulted upregulated after TAp73 silencing, stronger effect was seen after 48h (**Fig. 2C**). Similarly western blot (WB) analysis showed BNIP3 protein accumulation after TAp73 depletion (**Fig. 2D**). Together with the data reported in **Figure 1**, these data proved a TAp73-dependent inhibition of *BNIP3* expression in an oxygen-independent manner.

TAp73 binds BNIP3 promoter

The ability of TAp73 to inhibit the expression of *BNIP3* in an oxygen-independent manner indicated the possibility of an additional HIF-independent regulation of BNIP3 by TAp73. We therefore investigated the hypothesis that TAp73 acts also as a transcriptional factor directly regulating BNIP3 promoter. In support of this hypothesis BNIP3 has been shown as a direct p53 transcriptional target.[90] We therefore assessed whether the previous validated p53RE in *BNIP3* promoter could also be regulated by TAp73 (**Fig. 3A**). The p53RE is located between −987 and

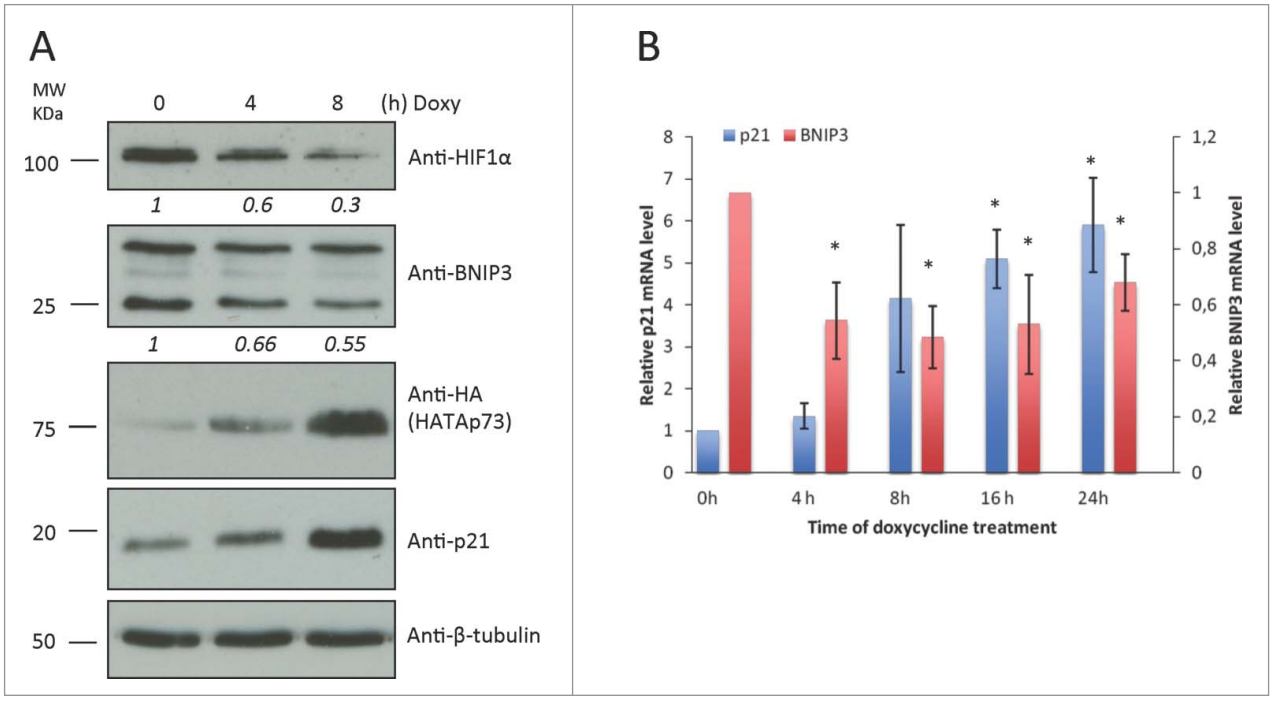

Figure 1. TAp73 overexpression inhibits *BNIP3* expression in ostesarcoma cell line. HATAp73 was overexpressed in SAOS2-HATAp73 cell line for 4h, 8h, 16h, 24h. (**A**) Protein levels of HIF1α, HATAp73, p21, BNIP3 and β-tubulin were analyzed by WB. Figure shows a representative replicate of 3 independent experiments. (**B**) mRNA levels of p21 and BNIP3 were analyzed by qPCR at different time points after TAp73 induction. Relative expression of genes was normalized against TBP and calculated as fold induction on the time point 0h. Data is reported as mean ± s.d. of two experiments for p21, 3 experiments for BNIP3. *$P < 0.05$ (Student's T-test).

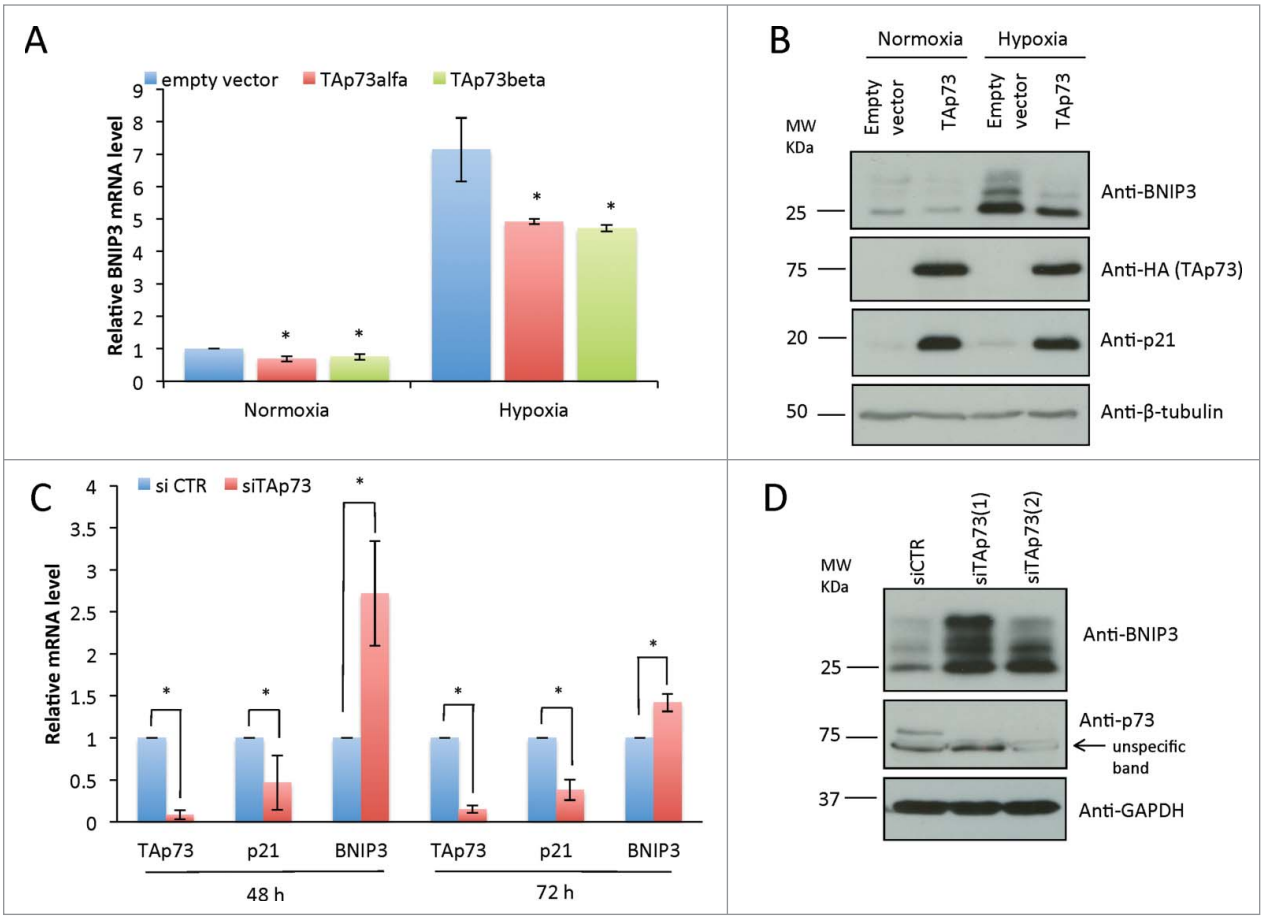

Figure 2. TAp73 inhibits *BNIP3* expression in non-small cell lung carcinoma cell line. (**A, B**) H1299 cells were transfected with HATAp73-alfa for 24h. Cells were subjected to hypoxia for 8h before lysis. (**A**) BNIP3 mRNA level was analyzed by qPCR. Data is reported as mean ± s.d., n = 3 independent experiments for hypoxia, n = 5 for normoxia. (**B**) Protein level of BNIP3, HATAp73 and p21 was analyzed by WB. (**C**) BNIP3 mRNA level was analyzed by qPCR after TAp73 knockdown in H1299 for 48h or 72h. n = 3. (**D**) Protein level of BNIP3 and p73 after 48h of TAp73 knockdown was analyzed by WB. (**A, C**) Relative expression of genes was normalized against TBP and calculated as fold induction. Data is reported as mean ± s.d. **P* < 0.05 (Student's T-test). (**B, D**). Figure shows a representative replicate of 3 independent experiments.

−1021 bp upstream of the transcription start site (TSS) and comprises 2 closely located p53 binding sites. To experimentally validate our hypothesis we used a reporter gene vector, containing the region of *BNIP3* promoter showed in **Fig. 3A** (between −1638 and +186 bp from the TSS) upstream of the luciferase reporter gene. We co-transfected H1299 cells with this construct, HA-TAp73-expressing plasmid and control Renilla vector for 20 h. Transfection efficiency was confirmed by WB (**Fig. 3C**). Consistently with our hypothesis luciferase assay showed significant decrease in luciferase activity of approximately 40% after HATAp73 transfection (**Fig. 3B**).

Next, we performed chromatin immunoprecipitation (ChIP) assay for the indicated p53RE in the *BNIP3* promoter, in TAp73 SaOs-2 Tet-On cells, after 16 h of doxycycline induction. The specific amplification in anti-HA immunoprecipitated chromatin confirmed a direct binding of TAp73 on BNIP3 human promoter (**Fig. 3D**). Data obtained from luciferase gene reporter assay and ChIP demonstrated that TAp73 suppresses *BNIP3* gene expression directly binding its promoter.

The BNIP3 regulation is of clinical importance for lung cancer patients

Trp73$^{-/-}$ and TAp73$^{-/-}$ mice spontaneously develop lung carcinomas, and altered ratio TAp73/ΔNp73 is frequently reported in human lung cancer.[91,92] TAp73 is therefore considered *a bona fide* tumor suppressor, particular relevant in lung tumorigenesis. We wanted therefore to verify whether downstream to TAp73 alteration, BNIP3 upregulation might play a role in lung carcinoma. We employed a bioinformatic approach to assess BNIP3 expression in human lung cancer patient specimens. We used publicly available Hou Lung patient data set to analyze BNIP3 expression in 156 patient samples. Dataset includes 4 groups of patient samples: derived from normal lung, large cell lung carcinoma, lung adenocarcinoma or squamous cell lung carcinoma. Median BNIP3 expression was significantly higher in all lung carcinomas compared to normal lung tissue (**Fig. 4A–C**). These data suggest that failure of TAp73/BNIP3 axis in lungs may lead to BNIP3 upregulation and may contribute to tumorigenicity.

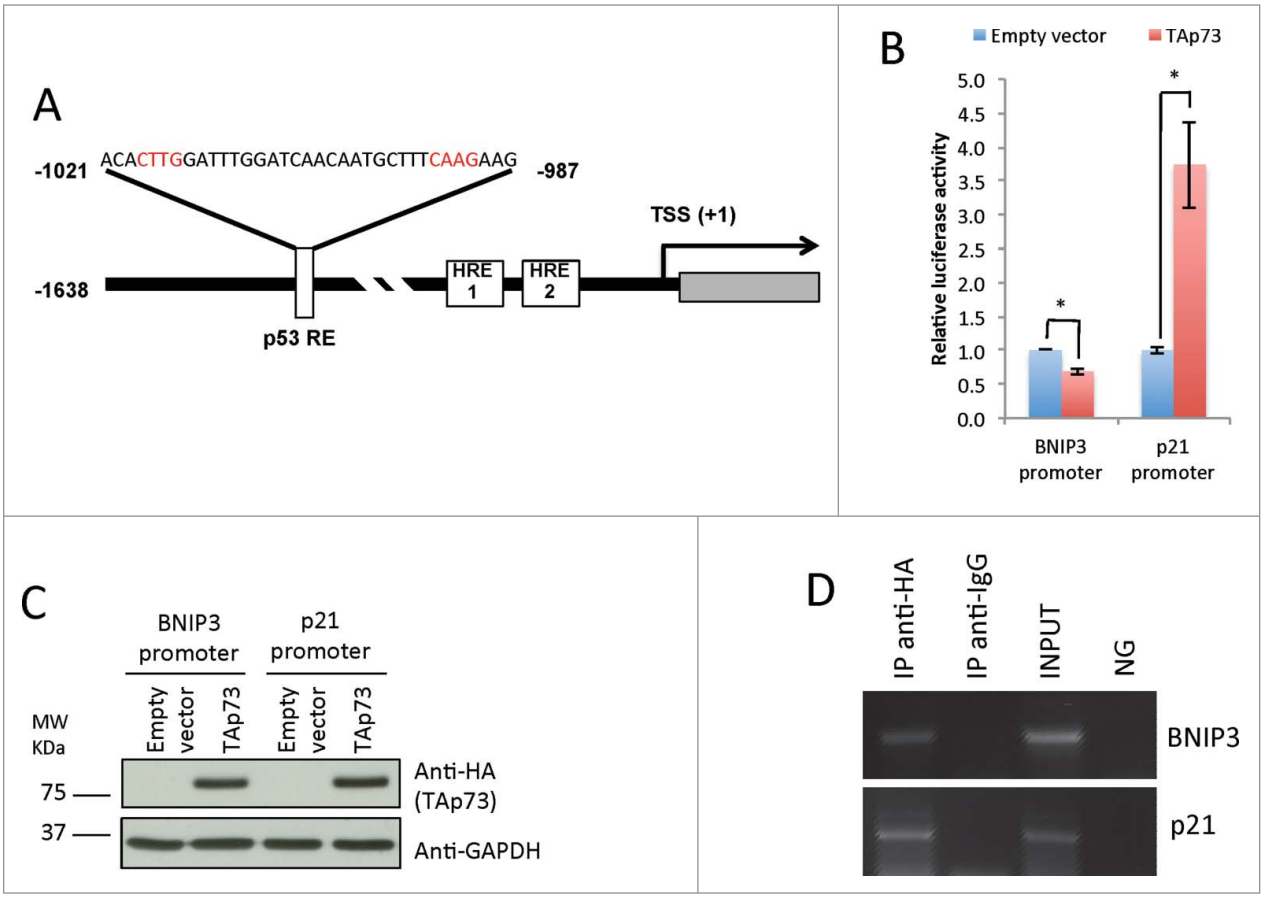

Figure 3. TAp73 directly transactivates p53 response element in the *BNIP3* promoter. (**A**) Schematic image of the *BNIP3* promoter region. HRE1, HRE2 – Hypoxia Response Elements. The insert shows p53 responsive element (p53RE), identified by Xi Feng et al.[90] located between −1021 and −987 bp upstream of the transcription-start site (TSS). Core p53 binding elements are highlighted in red. (**B**) BNIP3 promoter activity is repressed by TAp73. H1299 cells were cotransfected with BNIP3 reporter vector and pcDNA or TAp73 as a transactivator. The luciferase assay was performed after 20 h, and normalized by Renilla luciferase activity. Experiment was performed 2 times, mean value ± SD is shown. *$P < 0.05$ (Student's T-test) (**C**) Western Blot analysis performed with the same lysates which were used for Luciferase assay was used as a control of the TAp73 expression. (**D**) Chromatin extracted from SAOS2-HA-TAp73 was incubated with anti-HA or IgG antibodies. Immunoprecipitated DNA was tested by PCR for p53-Response Element in BNIP3 promoter. NG: PCR negative control. Figure shows a representative replicate of 3 independent experiments

We next used publicly available data set to assess BNIP3 expression impact on patients' survival. Survival rate appeared significantly higher in patients with low BNIP3 expression (**Fig. 4D**). Our data suggest that BNIP3 may have a role in tumorigenesis and progression of lung cancers.

Discussion

We identified *BNIP3* as a novel TAp73 target gene. BNIP3 expression can be regulated by TAp73 via 2 mechanisms (**Fig. 5**). Here we show that *BNIP3* expression is inhibited by TAp73, through its direct binding on BNIP3 promoter. We demonstrated that the p53-like responsive element in the *BNIP3* promoter, previously experimentally validated for p53 can also be recognized by TAp73. As *BNIP3* is a HIF1α target gene,[90] and HIF1α is repressed by TAp73,[41] relationship between TAp73 and BNIP3 can also depend on an indirect regulation via HIF1.

TAp73 has tumor-suppressor function, we therefore also investigated a possible involvement of BNIP3 in tumourigenesis. BNIP3 contributes to several processes in cell, which potentially can affect tumor development. The ability to activate apoptosis would indicate a tumor suppressor function for BNIP3, however its pro-necrotic role may lead to pro-tumorigenic effects, as necrosis can promote tumor growth and associates with poor prognosis for patients.[93] BNIP3 is also known to lead to autophagy, which may promote both tumor suppression and tumor growth, and the implication of autophagy in cancer progression can be different.[94-99] BNIP3 has also been shown to act as a transcriptional factor: if it translocates to nucleus, it suppresses Apoptosis-Inducing Factor expression, preventing cell death, thus showing tumorigenic function.[85] Our bioinformatics analysis would suggest an oncogenic function for BNIP3. BNIP3 expression is upregulated in lung carcinomas, and correlates with bad prognosis for patients with lung cancer. Therefore our current data, although still preliminary, might indicate TAp73/*BNIP3* negative axis as a novel pathway for TAp73 tumor suppressor

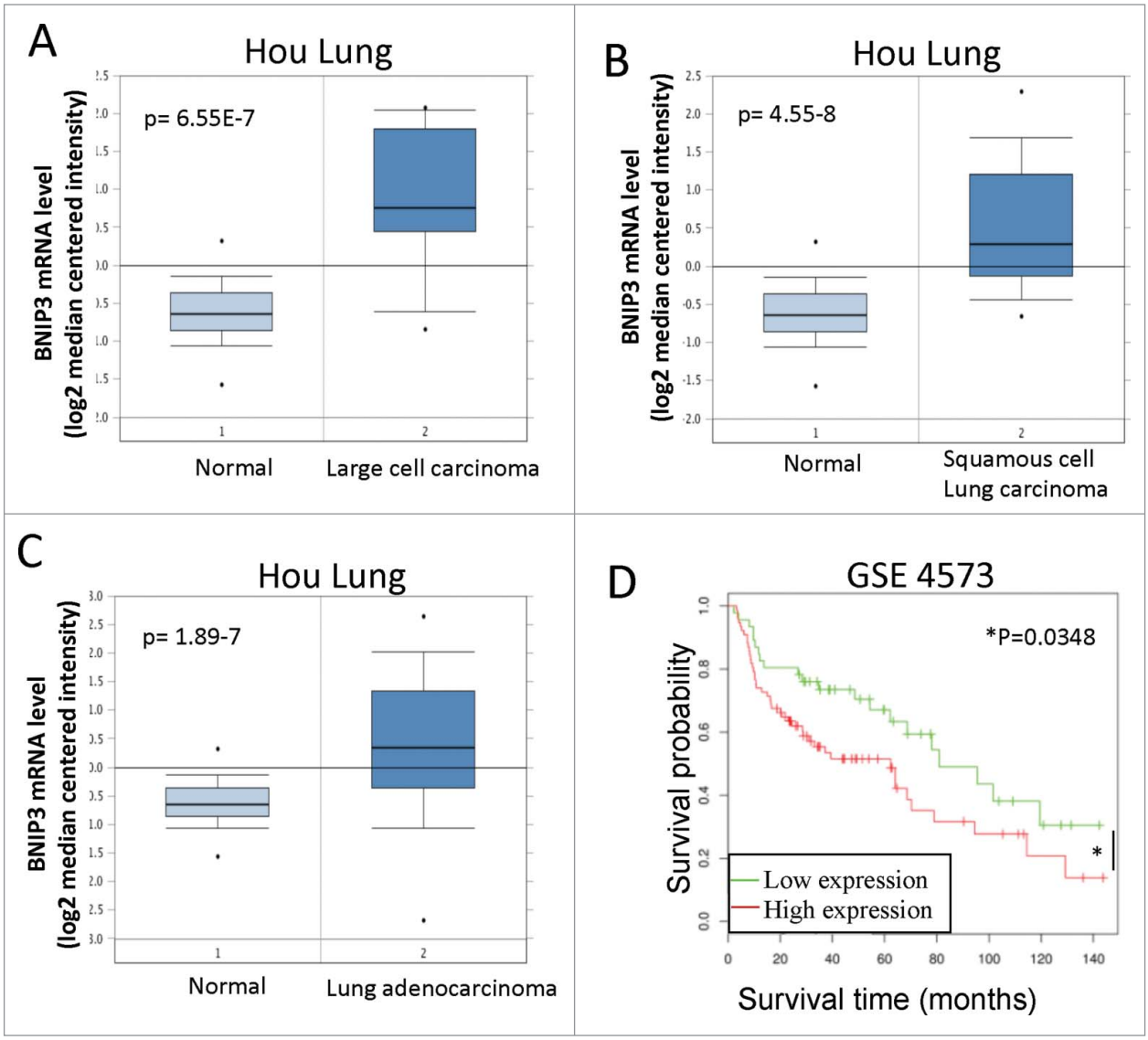

Figure 4. *BNIP3* expression is increased in lung carcinomas and correlates with worse patient survival. (**A**) *BNIP3* expression in normal lung and large cell carcinoma, Hou Lung dataset. (**B**) *BNIP3* expression in normal lung and squamous cell lung carcinoma, Hou Lung data set. (**C**) *BNIP3* expression in normal lung and lung adenocarcinoma, Hou Lung dataset. (**A–C**) n = 156 samples in th Hou Lung data set. (**D**) Survival analysis of GSE 4573 dataset (patients with lung cancer). Patients were divided in 2 groups: patients with low expression of the *BNIP3* gene and with high expression. n = 46 patients with low BNIP3 expression, n = 77 patients with high BNIP3 expression.

function. Consistently, TAp73 loss results in mitochondrial dysfunction.[100,101] BNIP3 upregulation as a consequence of TAp73 loss might therefore contribute to TAp73–dependent mitochondrial phenotype and be associated to the complex involvement of p73[102-104] and the other family members in regulation of mitochondrial activity,[105-108] cell metabolism[109-114] and redox homeostasis.[115-118] However, currently it is still unclear whether the complex integration of all the p53 family members, in particular the truncated isoform of p73, ΔNp73, and the cancer-associated mutants of p53, impacts and affects the TAp73-dependent antagonism of BNIP3 expression and more generally of hypoxia response. Future studies are demanded to address these aspects.

Overall, we described a novel transcriptional target of TAp73, also involved in hypoxia response, confirming the antagonistic role of TAp73 on HIF signaling and tumourigenesis.

Materials and Methods

Cell cultures

H1299 and SaOS2-Tet-On cell lines were used. Cells were grown in humidified incubator, at 37°C, in atmosphere of 5% CO_2 in air. Cells were cultivated in RPMI medium, containing L-glutamine, 4,5 g/L of D-glucose, 2,383 g/L of HEPES Buffer, 1,5 g/L of Sodium Bicarbonate, 110 mg/L of Sodium Pyruvate

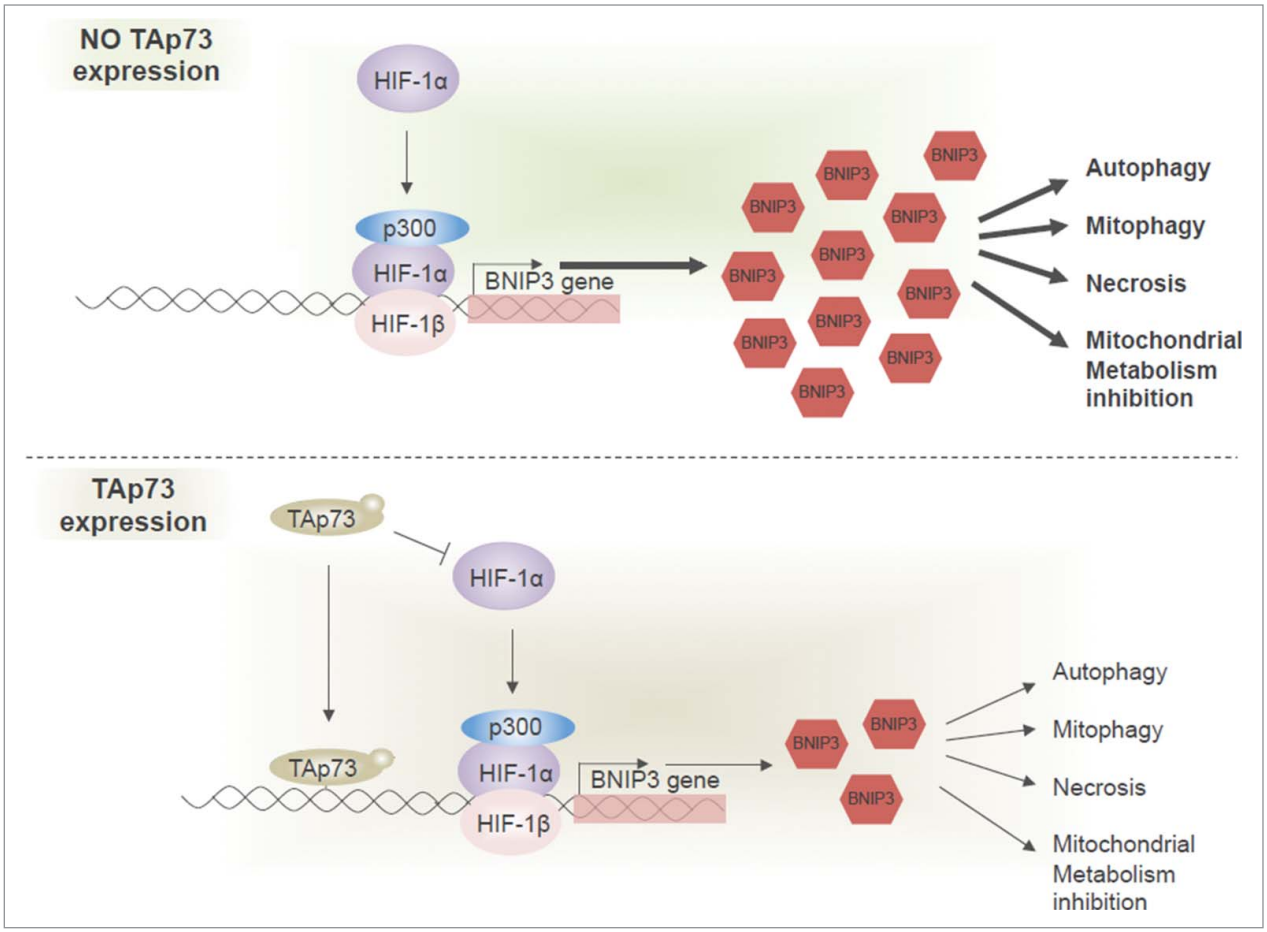

Figure 5. TAp73 regulates the *BNIP3* expression via 2 mechanisms. TAp73 can directly bind the *BNIP3* promoter and inhibit its expression. BNIP3 is upregulated by HIF1 in hypoxia. TAp73 drives HIF1α degradation and, subsequently, can prevent BNIP3 upregulation. No expression of TAp73 enables expression of BNIP3 (upper panel). TAp73 expression leads to lower BNIP3 level impacting different processes, including autophagy, mitophagy, mitochondrial metabolism and necrotic cell death.

(Gibco, Life Technologies), supplemented with Penicillin Streptomycin (Gibco, Life Technologies) and 10% (vol/vol) of FBS (Labtech). To generate SaOS2 cell line with inducible expression of HA-TAp73(SaOS2-Tet-On), we used Tet-responsive transcriptional activator rtTA. To induce HA-TAp73 expression in that cell line we treated the cells with 2 ug/ml of doxycycline for indicated period of time.

RNA extraction and quantitative PCR

RNA was extracted from cells by means of RNEasy Mini Kit (Qiagen), according to the Qiagen company protocol. The RNA obtained was quantified by spectrophotometric analysis, and 1 ug of total RNA was used to prepare cDNA with RevertAid H minus First Strand cDNA Synthesis kit (ThermoScientific), using Random primers and protocol from the kit. qPCR was carried out with 1/10 of prepared cDNA and Power SYBR Green PCR Master Mix (Applied Biosystems). Relative gene expression was analyzed in accordance to 7500 Software version 2.0.6 of Applied Biosystems, normalized to housekeeping gene TBP. Sequences of the primers used for the qPCR are: human TAp73: Fw CAGACAGCACCTACTTCGACCTT, Rev CCGCCCACCACCTCATTA; P21: Fw cctgtcactgtcttgtaccct; Rev gcgtttggag tggtagaaatct; TBP: Fw TCAAACCCAGAATTGTTCTCCTTAT; Rev CCTGAATCCCTTTAGAATAGGGTAGA; BNIP3: Fw cctgtcgcagttgggttc; Rev gaagtgcagttctacccaggag.

Western blot analysis

For the protein extraction cells were lysed in RIPA buffer with protease inhibitor cocktail tablets Complete, EDTA-free (Roche) and phosphatase inhibitor cocktail tablets PhosSTOP (Roche). Lysate was measured for protein concentration by using Bio-RAD Protein Assay (Bio-RAD), then mixed with Laemmly loading buffer, and 100 ug of proteins were loaded on 10% SDS-PAGE, and then transferred to polyvinylidene difluoride blotting membranes (Amersham, GE Healthcare). Membranes were blocked for 1 hour in 5% (m/vol) dry milk dissolved in PBS with 1% (vol/vol) Tween-20 (PBST); incubated with primary antibodies overnight and with secondary ones, conjugated with

horseradish peroxidase, for 1 hour. Antibodies were diluted in 5% dry milk in PBST: anti-HIF1α 1:250 (Novus Biologicals), anti-HA 1:1000 (Covance), anti-GAPDH 1:40000 (Sigma), anti-p21 1:1000 (Santa Cruz Biotechnology), anti-BNIP3 1:600 (Abcam), anti-β-tubulin 1:3000 (Santa Cruz Biotechnology), anti-P73 1:2000 (Bethyl). SuperSignal West Dura Chemiluminescenr Substrate (Thermo Scientific) was used to detect signal on membranes.

Cell transfection

For TAp73 overexpression in H1299 cell line 1.2 E6 cells were seeded per 10 cm dish 24 h before transfection. Transfection was performed with 10 ug DNA (pcDNA empty or pcDNA with HA-TAp73) per 10 cm dish using Lipofectamine 2000 Reagent (Invitrogen). Cells were collected 24 h after transfection.

For TAp73 knockdown in H1299 cell line 1.2 E6 cells were seeded per 10 cm dish 24 h before transfection. Transfection was performed using 50 nM siRNA (control siRNA (Ambion) or siTAp73 (Ambion)) and Lipofectamine RNAiMAX (Invitrogen). Each dish was split in two 24 h after transfection; cells were collected 48 h and 72 h after transfection.

For luciferase assay H1299 cells were seeded 20 h before transfection in 12-well plates, 1.5 E5 cells per well. Transfection was carried out by means of Lipofectamine 2000 (Invitrogen). Cells were cotransfected with 0.05 ng/well pcDNA with HA-TAp73 plasmid or empty pcDNA plasmid, 1 ug/well pRL-cytomegalovirus vector and 800 ng/well BNIP3 promoter luciferase reporter vector or p21 promoter luciferase reporter vector.

Luciferase assay

Cells were lyzed 20 h after transfection, and Firefly luciferase activity was measured, normalized to Renilla luciferase activity with Dual-Glo Luciferase Assay System (Promega), in accordance with Dual-Glo Luciferase Assay System protocol. Light emission over 1s was measured with luminometer.

Chromatin immunoprecipitation assay

SaOS2-Tet-On cell line was used for ChIP assay. TAp73 overexpression for 24 h was achieved by doxycycline treatment. Then cells were collected, fixed in 37% formaldehyde, and subjected to sonication for DNA shearing. Chromatin was immunoprecipitated with anti-HA antibodies (Covance) or unspecific immunoglobulin G (IgG) antibodies (Invitrogen) with a ChIP assay Kit (Invitrogen), and the promoter region, containing potential p73 response element, was amplified using the designed BNIP3 promoter primers. For positive control p21 promoter primers were used. The sequences of BNIP3-ChIP primers are following: 5′ -AGCGTTTCTGGGGCGCACCTTG- 3′ and 5′ -GGGACTGGGAGGCACTTTTCAGAGGA- 3′.

Bioinformatic analyses

By using Oncomine®database and Oncomine®Research Edition (available via Internet https://www.oncomine.org/resource/main.html) we gained access to Hou Lung dataset, analyzed it for BNIP3 expression and compared BNIP3 expression in normal lung with expression in large cell carcinoma, squamous cell lung carcinoma or lung adenocarcinoma.

Gene expression data set GSE4573 was downloaded. Patients were divided in 2 cohorts, in accordance to level of the BNIP3 expression. Kaplan-Meier curves, demonstrating survival, were built up for both cohorts. P-value is measured by Students t-test.[119,120]

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Supplemental Material

Supplemental data for this article can be accessed on the publisher's website.

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