**Tumor and Stem Cell Biology**

### p53-Dependent Regulation of Mitochondrial Energy Production by the RelA Subunit of NF-κB

Renée F. Johnson, Ini-Isabée Witzel, and Neil D. Perkins

#### Abstract

Aberrant activity of the nuclear factor kappaB (NF-κB) transcription factor family, which regulates cellular responses to stress and infection, is associated with many human cancers. In this study, we define a function of NF-κB in regulation of cellular respiration that is dependent upon the tumor suppressor p53. Translocation of the NF-κB family member RelA to mitochondria was inhibited by p53 by blocking an essential interaction with the HSP Mortalin. However, in the absence of p53, RelA was transported into the mitochondria and recruited to the mitochondrial genome where it repressed mitochondrial gene expression, oxygen consumption, and cellular ATP levels. We found mitochondrial RelA function to be dependent on its conserved C-terminal transactivation domain and independent of its sequence-specific DNA-binding ability, suggesting that its function in this setting was mediated by direct interaction with mitochondrial transcription factors. Taken together, our findings uncover a new mechanism through which RelA can regulate mitochondrial function, with important implications for how NF-κB activity and loss of p53 can contribute to changes in tumor cell metabolism and energy production. *Cancer Res; 71(16); 1–10. ©2011 AACR.*

#### Introduction

Aberrant activation of the nuclear factor kappaB (NF-κB) transcription factor family together with their activators, the IkB kinases (IKK), is associated with many human diseases, including cancer, in which it has been shown to regulate many tumor cell characteristics, including survival, proliferation, and metastasis (1, 2). There are 5 members of the NF-κB family RelA (p65), RelB, c-Rel, p50/p105, and p52/p100 that form homo- and heterodimers (3). Although there are considerable data supporting the role of NF-κB, particularly RelA, in the regulation of cancer cell survival, there is little information on the possible roles of NF-κB in the regulation of cell metabolism.

Interest in altered tumor cell metabolism was instigated by Otto Warburg’s hypothesis that a defect in cellular respiration and subsequent shift to glycolysis was the initiating step in tumorigenesis (4). One mechanism that can lead to this state is loss of the tumor suppressor p53, which results in decreased oxygen consumption and increased glycolysis (5). Interestingly, this glycolytic effect can be dependent on the NF-κB family member RelA, which in the absence of p53 resulted in enhanced expression of the glucose transporter Glut3 (6).

RelA, together with IKK subunits, has also been identified as a mitochondrial protein (7–10). Mitochondria contain an approximately 17-kb circular genome that codes for 13 proteins, 22 tRNAs, and 2 ribosomal RNAs (Supplementary Fig. S2A), all of which are involved in oxidative phosphorylation (11). There are 3 mitochondrial transcripts. Transcription of the light strand produces a single mRNA encoding ND6 and 8 tRNA sequences. The heavy strand produces an RNA encoding the 2 mitochondrial rRNA sequences, 12S and 16S rRNA, together with a transcript encoding the remaining 12 mRNAs, 14 tRNAs, and the 2 rRNAs, which then undergo subsequent RNA splicing to generate separate RNA species (12). NF-κB can repress mitochondrial gene expression, including cytochrome B and cytochrome C oxidase mRNA levels, following TNF or TNF-related apoptosis-inducing ligand (TRAIL) stimulation (8, 9), although the mechanism through which this was accomplished, or whether this was a direct effect of specific NF-κB subunits, was not established. Moreover, the mechanism and consequences of NF-κB mitochondrial localization on oxidative phosphorylation and ATP production, together with how these might contribute to the switch to glycolysis observed in cancer cells, have not been clearly defined.

#### Materials and Methods

**Cells**

RelA−/− mouse embryo fibroblast (MEF) cells [provided by Professor Ron Hay (University of Dundee)] were reconstituted...
by lentiviral infection with vector alone (null) or with human RelA as described previously (13). H1299wtP53 cells have been previously described (14, 15). H1299 cells were purchased directly from the American Type Culture Collection, and older stocks of H1299 cells were verified against the new cells at the Health Protection Agency by microsatellite genotyping. U-2 OS and PC3 cells were purchased directly from the European Collection of Cell Cultures and were grown in Dulbecco's modified Eagle's medium as previously described (14, 15). H1299 cells were purchased directly from the American Type Culture Collection, and older stocks of H1299 cells were verified against the new cells at the Health Protection Agency by microsatellite genotyping. U-2 OS and PC3 cells were purchased directly from the European Collection of Cell Cultures and were grown in Dulbecco's modified Eagle's medium as previously described (14, 15). All cells were grown to a maximum confluency of 70% and were modified Eagle's medium as previously described (14, 15). H1299 cells were purchased directly from the American Type Culture Collection, and older stocks of H1299 cells were verified against the new cells at the Health Protection Agency by microsatellite genotyping. U-2 OS and PC3 cells were purchased directly from the European Collection of Cell Cultures and were grown in Dulbecco's modified Eagle's medium as previously described (14, 15). All cells were grown to a maximum confluency of 70% and were split 1:5 (U-2 OS, PC3, and H1299 cells) or 1:10 (RelA cells) every 3 to 4 days for a maximum of 25 passages. It should be noted that the RelA<sup>−/−</sup> MEF cells used in these studies possess a mutant form of p53 (16). In the text, "early" refers to passages 4 to 13 whereas "late" refers to passages 16 to 25, with cells in the "transition" period not being used. Individual experiments used a mix of cells with different passage numbers within these "early" and "late" periods.

Isolation of mitochondrial proteins
Mitochondrial proteins were isolated from the cells using the ProteoExtract Cytosol/Mitochondria Fractionation Kit (Calbiochem) following the manufacturer's instructions. Mitochondria were further purified by centrifugation through a 19% (v/v) Percoll gradient (Sigma).

Measurement of ATP levels
ATP levels from 5,000 cells per sample were measured using the CellTitre-Glo Luminescent Cell Viability Assay (Promega) following the manufacturer's instructions. Luminescence was measured following 2-hour incubation with a FLUOstar Omega microplate reader (BMG Labtech). Results were expressed as average relative luciferase units (RLU) per cell.

Measurement of oxygen consumption
Oxygen consumption from 50,000 cells per sample was measured in a 96-well BD Oxygen Biosensor system (BD Biosystems) following the manufacturer's instructions. Fluorescence was measured after a 5-hour incubation with a FLUOstar Omega microplate reader at excitation of 485 nm and emission of 630 nm. Data were expressed as normalized relative fluorescence (NRF) relative to a blank measurement for each individual well in the absence of cells and media.

Other assays
DNA/siRNA transfections, immunoprecipitations, Western blotting, chromatin immunoprecipitation (ChIP), and quantitative real-time reverse transcriptase PCR were carried out as described (14, 17, 18). All experiments were conducted with a minimum of 3 repeats.

Data analysis and statistics
In all figures, oxygen consumption data are shown as mean ± SD NRF and expressed relative to the control samples. ATP data are shown as mean ± SD RLU/cell and expressed relative to the control sample. mRNA data are shown as mean ± SD normalized relative to 18s mRNA, and ChIP data are shown as mean ± SD normalized to input and expressed relative to the Gal4 control. All Western blottings are representative of a minimum of 3 individual experiments. Band intensity was quantified using NIH ImageJ software and is shown in Supplementary Table S1. Statistical comparisons between groups were analyzed by Student’s t test, or where appropriate, the paired t test. Comparisons between more than 2 groups were analyzed using one-way ANOVA followed by a Tukey-Kramer multiple comparisons test. Significance was determined at P<0.05. For all data, * indicates P<0.05, ** indicates P<0.01, and *** indicates P<0.001.

Results

Regulation of oxygen consumption and ATP levels by RelA
To investigate any potential role for RelA as a regulator of oxidative phosphorylation and cellular energy production, the consequences of RelA depletion by RNA interference were examined in the U-2 OS osteosarcoma cell line. These cells, in common with many other transformed and immortalized cell lines, have a basal level of IKK and NF-κB activity (19), so these experiments were carried out without an additional NF-κB activating stimulus. Interestingly, the effect of RelA knockdown varied dependent upon the time spent in culture, with increased passage of U-2 OS cells resulting in a switch from a decrease to an increase in oxygen consumption upon RelA depletion (Fig. 1A). For ease of interpretation, the control levels in earlier and later passage cells have both been normalized to 1 but absolute levels are given in the figure legend. Addition of the antibiotic oligomycin, which inhibits the mitochondrial H<sup>+</sup>-ATP synthase, strongly inhibited cellular oxygen consumption in late-passage U-2 OS cells, confirming that these measurements derive from mitochondrial oxidative phosphorylation (Fig. 1B). Moreover, under these conditions, no increase in oxygen consumption following RelA knockdown was seen, further confirming NF-κB regulation of cellular respiration (Fig. 1B).

To determine whether these changes in oxidative phosphorylation resulted in changes in cellular ATP levels, we examined U-2 OS cells following RelA knockdown. As with oxygen consumption, the effect seen proved dependent upon the time the cells had spent in culture. RelA knockdown in earlier passage human U-2 OS osteosarcoma cells inhibited ATP production, whereas RelA knockdown in later passage cells resulted in increased ATP production (Fig. 1C). Similar results were seen with knockdown of RelA in PC3 prostate cancer cells, confirming the generality of this observation (Supplementary Fig. S1A). Endogenous RelA has previously been shown to be mitochondrially localized in these cells (9).

Cancer cells derive the majority of their ATP production from glycolysis. We were therefore interested in determining whether these changes in ATP levels resulted from the effects seen on oxygen consumption. Interestingly, treatment of later passage U-2 OS cells with oligomycin did not significantly change ATP levels in control cells, suggesting that, as
predicted, ATP production comes primarily from glycolysis. However, oligomycin treatment did prevent the increase in ATP seen upon RelA knockdown, indicating that this effect results from RelA repression of oxidative phosphorylation (Fig. 1D). Consistent with this, we saw no significant RelA-dependent change in glucose consumption in late-passage U-2 OS cells (Supplementary Fig. S1B).

Large fluctuations in fundamental aspect of cell metabolism, such as in ATP levels and oxygen consumption, are not to be expected. Nonetheless, to confirm the functional significance of these effects, we investigated downstream effects of these changes by analyzing the energy-sensing protein, 5′-AMP-activated protein kinase α (AMPKα; ref. 20). Importantly, RelA knockdown differentially altered activatory Tyr172 phosphorylation of AMPKα, in a manner correlating with the effects of RelA on total ATP levels (Supplementary Fig. S1C), indicating that these changes were physiologically significant.

RelA binds to mitochondrial DNA and regulates mitochondrial transcription

We were interested in whether mitochondrially localized RelA was a cause of these effects on oxygen consumption and ATP levels. We confirmed the presence of RelA in mitochondrial protein preparations from U-2 OS cells, with higher levels being seen in later passage cells (Supplementary Fig. S2A). Because RelA is a DNA-binding protein, one mechanism through which it could exert its effects on oxygen consumption and ATP levels is the regulation of mitochondrial gene expression. We therefore examined the binding of RelA to mitochondrial DNA (mtDNA) by ChIP. Mitochondrial gene transcription occurs bidirectionally from 3 promoters located in the D-loop region of the genome (Supplementary Fig. S2A). Consistent with the increased localization of RelA to mitochondria in later passage U-2 OS cells (Fig. 2A), significant binding of RelA to the D-loop promoter region of the mitochondrial genome was observed only in late-passage cells (Fig. 2B). Primers to the cytochrome
B region, which is immediately adjacent to the D-loop, confirmed this result (Supplementary Fig. S2B). Because of the resolution allowed by ChIP, this result does not imply that RelA is specifically binding to sites within the cytochrome B gene. Interestingly, there was a RelA-dependent decrease in the binding of POLRMT, the mitochondrial RNA polymerase, to mtDNA that was observed only in late-passage cells (Fig. 2C). To assay what effect this change in POLRMT binding may have on mitochondrial gene expression, quantitative PCR (qPCR) analysis was carried out using primers targeted to specific mitochondrially encoded genes. Significantly, a decrease in cytochrome B RNA and protein levels was also observed in later passage cells, which was partially reversed upon RelA depletion (Fig. 2D; Supplementary Fig. S2C). No significant effect of RelA knockdown on cytochrome B RNA levels was seen in the earlier passage cells. Similar, late-passage specific effects were seen for cytochrome C oxidase I and cytochrome C oxidase III (Supplementary Fig. 2D; data not shown).

Taken together, these results suggest that RelA effects on oxidative phosphorylation and ATP levels in earlier passage cells are not mediated directly through mitochondria and...
most probably result from regulation of nuclear gene expression. However, as the cells continue to grow in culture, a process generally associated with acquisition of a more transformed phenotype, RelA actively represses oxidative phosphorylation, at least in part through repression of mitochondrial gene expression.

**Mitochondrial RelA function requires its C-terminal transactivation domain**

To learn more about RelA function in mitochondria, we created a series of fusion proteins in which a mitochondrial targeting sequence (MTS) was fused to the N-terminus of RelA, thereby allowing the effects of mitochondrial RelA to be dissociated from nuclear and other cellular effects. In addition to full-length human RelA, MTS-tagged versions of a C-terminal deleted RelA, encoding the amino-terminal DNA binding and dimerization Rel homology domain (RHD), together with a specific DNA-binding mutation (DBM) of full-length RelA, were created. ChIP analysis of a non-MTS–tagged form of the RelA DBM mutant with primers to the IkBα promoter, a known NF-κB target (21), confirmed the loss of sequence-specific DNA-binding ability (Supplementary Fig. S3A). Western blot analysis confirmed that all MTS-tagged proteins were targeted to mitochondria (Supplementary Fig. S3B). Interestingly, all MTS-tagged forms of RelA, including the DBM mutant, were seen to bind mtDNA by ChIP analysis, with significantly higher levels of binding seen with the C-terminally deleted RelA RHD (Fig. 2E). This result suggests that RelA does not require direct binding to kB elements within the mtDNA and that recruitment can result indirectly through interaction with mitochondrial transcription factors.

Consistent with the data seen upon depletion of endogenous RelA (Fig. 2D), expression of exogenous, MTS-tagged RelA in U-2 OS cells, resulted in repression of cytochrome B and cytochrome C oxidase III RNA levels (Fig. 2F; Supplementary Fig. S3C) as well as a significant decrease in oxygen consumption and ATP levels (Supplementary Fig. S3D and E). None of these effects were seen upon expression of nontagged, wild-type RelA, confirming that MTS tagging can distinguish mitochondrial from other cellular effects of RelA. Repression of oxygen consumption by exogenously expressed MTS-tagged RelA but not wild-type RelA was confirmed in p53-null human non–small-cell lung carcinoma H1299 cells (Supplementary Fig. S3F). Consistent with these data and our previous analysis (Fig. 2C), expression of MTS-tagged RelA resulted in a decrease in POLRMT binding to mtDNA (Supplementary Fig. S3G).

Analysis of the MTS-tagged RelA mutants produced a surprising result. Although MTS-tagged RelA RHD binds mtDNA more efficiently than any other RelA construct (Fig. 2E), it failed to repress mitochondrial gene expression, oxygen, and ATP levels together with POLRMT binding (Fig. 2F; Supplementary Fig. 3C-E and G). In contrast, MTS-tagged RelA DBM exhibited all of these effects almost to the same levels as MTS-tagged wild-type RelA. Therefore, DNA binding and/or recruitment to the mitochondrial genome are not sufficient in itself to regulate oxidative phosphorylation and there is a requirement for the C-terminal RelA transactivation domain (TAD).

**p53 regulates RelA mitochondrial localization and function**

A number of positive and negative feedback loops between the p53 tumor suppressor and NF-κB pathways have been identified (22), and p53 suppresses NF-κB–dependent tumorigenesis in a murine lung cancer model (23). Furthermore, p53...
effects on glycolysis can be NF-κB dependent (6). We observed a decrease in p53 levels associated with increased growth of U-2 OS cells in culture, (Supplementary Fig. S4A). Therefore, we investigated whether p53 activity might also regulate RelA mitochondrial function. Significantly in both p53-null H1299 cells and in p53−/− MEF cells, used to avoid any issues with background levels of wild-type p53, reexpression of p53 reduced RelA levels in mitochondria (Fig. 3A and B) whereas, induction of p53 expression by isopropyl-β-D-thiogalactoside (IPTG) treatment of H1299wt53 cells (15; Supplementary Fig. S4B) resulted in loss of RelA binding to mtDNA as determined by ChIP analysis (Fig. 3C).

We next determined the consequences of the ability of p53 to regulate RelA mitochondrial localization. Consistent with p53-induced loss of mitochondrial RelA, siRNA depletion of endogenous RelA no longer resulted in an increase in cytochrome B or cytochrome C oxidase III RNA levels in either H1299 or p53−/− MEF cells in which p53 was reexpressed (Fig. 4A and B, Supplementary Fig. 4C–H). qPCR and Western blot analysis confirmed the effects of p53 on RelA did not result from changes in RelA protein or RNA levels (Supplementary Fig. S4B, D, E, G, and H).

These observations suggested that RelA-dependent changes in oxidative phosphorylation and ATP levels would also be p53 dependent. Indeed, induction of p53 expression in H1299wt53 cells abolished the increase in oxygen consumption and ATP levels seen upon siRNA depletion of endogenous RelA (Fig. 4C and D). Moreover, a complete reversal of RelA function was observed, with depletion of endogenous RelA now reducing the increase in oxygen consumption and ATP levels seen upon induction of p53. Importantly, similar contrasting effects of RelA on ATP levels were observed between wild-type or p53−/− MEF cells. Here, RelA knockdown in wild-type cells resulted in a decrease in ATP levels, whereas in the absence of p53, RelA knockdown had the opposite effect (Supplementary Fig. S4I).

Endogenous RelA is localized to mitochondria through an interaction with Mortalin

Although our results showed clear effects on RelA mitochondrial localization, the mechanism through which this is achieved and how this might be perturbed by p53 was not clear. RelA lacks a defined N-terminal MTS, suggesting transport to mitochondria through a distinct, rate-limited, mechanism to proteins exclusively or predominantly localized in this organelle. If RelA possessed a classical MTS, a disproportionate level of protein could become localized to this organelle. An indication of how this occurs resulted from separate analysis of proteins binding the region of threonine 505 (T505)
phosphorylation in the RelA TAD. Previously, we identified phosphorylation of RelA at T505 as an important regulatory site that can help determine cell fate by inhibiting antiapoptotic function of RelA (17, 18). To identify proteins binding to the evolutionarily conserved T505 region, we carried out peptide affinity chromatography with either a T505 region peptide or a scramble control peptide (Fig. 5A). Analysis of the eluted proteins revealed a 75-kDa protein that specifically bound the T505 peptide, identified by mass spectrometry as Mortalin (Fig. 5B). Western blot analysis of column fractions confirmed that Mortalin was present only in the samples from the T505 peptide columns (Fig. 5C). Importantly, immunoprecipitation of endogenous RelA showed binding to endogenous Mortalin in HeLa, U-2 OS, and HEK 293 cells (Fig. 5C and D). We next analyzed the effect of mutating the RelA T505 residue to alanine using RelA<sup>T505A</sup> immortalized MEF cells

![Figure 5](https://example.com/figure5.png)

**Figure 5.** The HSP70 family member Mortalin is a RelA-binding protein. A, the RelA T505 region in the TAD is highly conserved across species. A peptide spanning this region (T505 peptide) and a control scramble peptide (scramble) were used to identify binding partners of this region by peptide affinity chromatography. B, a 75-kDa protein from HeLa whole-cell extracts that bound to the T505 peptide was identified by mass spectrometry as Mortalin. C, Western blotting (WB) of eluted column fractions confirming Mortalin binding to the RelA T505 motif peptide (top) and coimmunoprecipitation of endogenous RelA with Mortalin from HeLa cell extracts (bottom). D, coimmunoprecipitation of endogenous RelA with Mortalin from U-2 OS and HEK 293 whole-cell extracts. Mouse IgG (mIgG) was used as a control in the immunoprecipitation (IP). E, in RelA<sup>T505A</sup> MEF cells reconstituted with RelA or a RelA T505A mutant, Mortalin was immunoprecipitated from whole-cell lysates, followed by subsequent Western blotting. F, mitochondria were isolated from RelA<sup>T505A</sup> MEF cells reconstituted with RelA or RelA T505A mutant, followed by Western blot analysis. G, ChIP analysis of RelA binding to the D-loop region of the mitochondrial genome in RelA<sup>T505A</sup> MEF cells reconstituted with RelA or RelA T505A mutant (P < 0.01, n = 5/group).
reconstituted with wild-type and mutant forms of RelA, to overcome background interactions from wild-type RelA. Confirming the specificity of this interaction, T505A-mutated RelA no longer coimmunoprecipitated with Mortalin (Fig. 5E).

Mortalin, also known as mitochondrial HSP70, is a member of the HSP-70 family that plays an important role in a number of cellular processes, including the stress response, cellular proliferation, intracellular trafficking, antigen processing, differentiation, and tumorigenesis (24, 25). Mortalin is known to act as a molecular chaperone facilitating protein unfolding and transport across the mitochondrial inner membrane through interaction with translocase of inner membrane (TIM) proteins (26–28), although it can also be found in the cytoplasm of certain cell types (29). We were therefore interested in whether this interaction with Mortalin provided a basis for RelA mitochondrial localization and function.

Consistent with this hypothesis, the RelA T505A mutant also displayed reduced mitochondrial localization (Fig. 5F) and failed to bind mtDNA, as determined by ChIP analysis (Fig. 5G; Supplementary Fig. S5A). Furthermore, siRNA knockdown of Mortalin in U-2 OS and H1299 cells resulted in reduced levels of mitochondrial RelA (Fig. 6A; Supplementary Fig. S5B) and reduced binding of endogenous RelA to mtDNA as determined by ChIP analysis (Fig. 6B), whereas overexpression of Mortalin resulted in increased levels of endogenous mitochondrial RelA (Fig. 6C). Taken together, these data indicated that mitochondrial RelA localization is mediated by an interaction between the T505 region of the RelA TAD and Mortalin.

Importantly, these data provided a potential explanation for the ability of p53 to exclude RelA from mitochondria, because it has been previously reported that Mortalin also binds p53 and can sequester it in the cytoplasm (30, 31). Consistent with this hypothesis, induction of p53 expression by IPTG treatment of H1299wtp53 cells resulted in reduced RelA binding to Mortalin (Fig. 6D).

These results indicate that RelA mitochondrial localization and function are dependent upon the p53 status of the cell,
with high p53 levels inhibiting RelA translocation to this organelle through inhibition of RelA association with Mortalin. As a consequence, p53 prevents RelA-dependent repression of mitochondrial gene expression and oxidative phosphorylation. However, RelA and p53 can also cooperatively promote oxidative phosphorylation through other mechanisms, most likely involving regulation of nuclear gene expression (Fig. 7).

Discussion

This study shows endogenous RelA binding to the mitochondrial genome and links this to regulation of oxidative phosphorylation. Such direct regulation of mitochondrial gene expression by normally nuclear transcription factors can potentially provide a mechanism to link the regulation of mitochondrial function with other cellular signaling pathways. We propose that this process contributes to the switch to glycolysis observed in cancer cells.

Our data suggest that p53 prevents RelA mitochondrial localization by inhibiting its interaction with Mortalin (Fig. 6D). Because p53 has itself been shown to bind to RelA and form a transcriptionally active complex upon stimulation with TNFα or replication stress (33), as well as interact directly with Mortalin (30, 31), this could be achieved through competitive binding and sequestration. However, other mechanisms are possible and our data also suggest that RelA mitochondrial import is regulated by posttranslational modification. This conclusion is implied from our identification of Mortalin as a protein binding the T505 region of RelA (Fig. 5), with the T505A mutation resulting in disruption of the RelA/Mortalin complex and inhibition of RelA mitochondrial localization (Fig. 5E–G). Although this suggests that phosphorylation at this site may be required to promote this interaction, a purely structural effect cannot be ruled out.

It is probable that the physiologic role of RelA in mitochondria is selective and that it will not regulate mitochondrial function in all cell types at all times. We propose that this is most likely to occur during NF-κB–dependent processes in vivo, coupling the physiologic response to the need for increased or decreased energy and ATP levels. For example, IKK/NF-κB signaling has been shown to affect mitochondrial function and biogenesis in skeletal muscle (34), whereas Guseva and colleagues showed that TRAIL activation of NF-κB DNA binding in mitochondria in LNCAP and PC3 prostate cancer cells resulted in repression of mitochondrial gene expression (9). We suggest that tumor cells (and the cell lines derived from them) that have become dependent upon NF-κB for their ability to grow and survive have subverted NF-κB mitochondrial function, where it contributes to the switch from oxidative phosphorylation to glycolysis, in part through fulfilling a negative regulatory role on mitochondrial gene expression.

Our results provide another mechanism linking the p53 and NF-κB pathways that will contribute to the ability of p53 to suppress the oncogenic characteristics of NF-κB (22) and inhibit NF-κB–dependent tumor growth (23). We propose that p53 loss during tumorigenesis removes an important control on RelA regulation of mitochondrial function, providing a pathway through which NF-κB can contribute toward cancer cell malignancy by fundamentally altering cellular metabolism.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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