UV-induced stress response involves expression change of a myriad of genes, which play critical roles in modulating cell cycle arrest, DNA repair, and cell survival. Alteration of micro RNAs has been found in cells exposed to UV, yet their function in UV stress response remains elusive. Here, we show that UV radiation induces up-regulation of miR-125b, which negatively regulates p38α expression through targeting its 3′-UTR. Increase of miR-125b depends on UV-induced NF-κB activation, which enhances miR-125b gene transcription upon UV radiation. The DNA damage-responsive kinase ATM (ataxia telangiectasia mutated) is indispensable for UV-induced NF-κB activation, which may regulate p38α activation and IKKβ-dependent IkBα degradation in response to UV. Consequentially, repression of p38α by miR-125b prohibits prolonged hyperactivation of p38α by UV radiation, which is required for protecting cells from UV-induced apoptosis. Altogether, our data support a critical role of NF-κB-dependent up-regulation of miR-125b, which forms a negative feedback loop to repress p38α activation and promote cell survival upon UV radiation.

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MicroRNAs (miRNAs) are a group of endogenous small non-coding RNAs (~23 nucleotides) that negatively regulate gene expression at the post-transcriptional level, mainly via binding to the 3’-untranslated region (3’-UTR) of target mRNA (15). The binding of miRNA-loaded RNA-induced silencing complex with target mRNA may lead to blockage of protein translation as well as reduced mRNA stability (16). In mammalian cells, the vast majority of miRNAs are encoded by RNA polymerase II as intergenic miRNAs or as introns of host protein-coding genes (17). In the nucleus, the ~70-nucleotide hairpin structures of primary miRNA gene transcripts, termed primary miRNAs, are recognized by RNase III endonuclease Drosha-DGCR8 microprocessor complex and cleaved into precursor miRNAs, which can be exported to the cytoplasm by exportin 5. In the cytoplasm, another RNase III endonuclease, Dicer, will further process precursor miRNAs to yield mature miRNAs, which can be loaded into RNA-induced silencing complex along with Argonaute (Ago) proteins for targeting mRNAs through interactions with sites of imperfect complementarity (18). It was shown that UV induced a cell cycle-dependent relocation of Ago2 into stress granules and altered miRNA expression in part dependent on ATM/ATR (13). However, whether UV radiation regulates miRNA expression by modulating their gene transcription or altering post-transcriptional maturation has not been determined.

Previous studies have suggested that NF-κB may play an important role in regulating transcription of miRNA genes (19–21). In this report, we found that miR-125b induction upon UV radiation was dependent on activation of NF-κB, which enhanced miR-125b gene transcription. ATM activation in response to UV-induced DNA damage was indispensable for NF-κB activation in cells exposed to UV radiation. Moreover, the up-regulated miR-125b directly targeted p38α and negatively regulated its expression, which prevented prolonged p38α activation and protected cells from p38α-mediated apoptosis upon UV treatment.

**EXPERIMENTAL PROCEDURES**

*Cell Culture, Plasmids, and Reagents—*Human embryonic kidney cell line HEK293, mouse embryonic fibroblast cells (wild type, IKKβ−/−, and ATM−/−), human colon cancer cell line HCT116 (wild type and Dicer−/−), and human osteosarcoma cell line U2OS were maintained in DMEM containing 10% fetal bovine serum. Human keratinocyte cell line HaCaT was grown in DMEM/F-12 medium supplemented with 10% fetal bovine serum. All cell lines were maintained in the presence of penicillin (100 IU/ml) and streptomycin (100 mg/ml) at 37 °C with 5% CO₂. The expression construct of pre-miR-125b was from Origene (Rockville, MD). Control (26164)

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**UV-induced miR-125b Targets p38α**

sponge construct obtained from Addgene and the strategy to generate miR-125b sponge have been described in a previous report (22). The expression construct of p38α was generated by cloning the coding region sequence of human p38α into pcDNA3 expression vector. To generate p38α miRNA-targeting reporter, p38α 3’-UTR was amplified from human genomic DNA and inserted downstream of the luciferase (Luc2) sequence of pmirGLO Dual-Luciferase reporter construct (Promega, Madison, WI) following the manufacturer’s instructions. A similar strategy was used to generate the miR-125b luciferase reporter by inserting synthesized miR-125b-target sequence into the pmirGLO reporter construct. Substitution mutants of p38α 3’-UTR were generated by QuickChange PCR. Antibodies against p38α, IKKβ, PARP1, caspase-8, or cleaved caspase-3 were from Cell Signaling Technology (Danvers, MA). Antibodies against 14-3-3σ, tubulin, and tubulin were from Santa Cruz Biotechnology, Inc. (Santa Cruz, CA). ATM inhibitor Ku55933, CK2 inhibitor TBB, and p38α inhibitor SB203580 were from EMD (Billerca, MA), and IKKβ inhibitor TP-53 was from Sigma. UV radiation was carried out with a GS Gene Linker UV chamber cross-linker (Bio-Rad).

**RNA Extraction and Quantitative Real-time PCR—**Total RNA was extracted from cells using TRIzol (Invitrogen) and then converted to first-strand cDNA using Superscript III transcriptase (Invitrogen). For microRNA analysis, total RNA was poly(A)-tailed using poly(A) polymerase (Ambion) before reverse transcription as described previously (23). The small noncoding RNA U6 and GAPDH were used as internal control for miR-125b, pri-miR-125b, and p38α quantitation, respectively, and quantitative real-time PCR was carried out as described previously (24). The sequences of gene-specific primers used for quantitative real-time PCR are listed in supplemental Table 1.

**Immunoblotting—**Total cell extracts were prepared and subjected to immunoblotting as described previously (25). For quantitation of the immunoblotting signal, IRdye-labeled secondary antibodies were used, and signals were analyzed by Odyssey scanner (LI-COR, Lincoln, NE).

**Luciferase Assay—**HEK293 cells were transfected with respective pmirGLO Dual-Luciferase reporter constructs harboring miR-125b target sequence or p38α 3’-UTR. After 36 h, cells were treated and lysed with passive lysis buffer, and the activity of firefly luciferase and Renilla luciferase in the lysates was measured with the Dual-Luciferase assay system (Promega). For the luciferase transcription reporter assay, NF-κB-Fluc2p (pGL4.32) from Promega was used as a positive control. hsa-miR-125b-1/2 gene reporters were generated by inserting the respective promoter regions (WT or κB site deletion) into pGL4.11 vector. HEK293 cells were transfected with transcription reporters along with Tk-Rluc reporter. Cells were mock-treated or treated with UV, and luciferase activity was measured as described above.

**Electrophoretic Mobility Shift Assay (EMSA)—**The Igκ-κB oligonucleotide probe and conditions for EMSA were described previously (24). The Oct-1 site oligonucleotide used for control was obtained from Promega. Gels were exposed and quantified with a Cyclone phosphor imager (PerkinElmer Life Sciences).
Chromatin Immunoprecipitation (ChIP)—ChIP assays were carried out as described previously (24). Briefly, treated cells were cross-linked with 1% formaldehyde, sheared to an average size of \( \lesssim 500 \) bp, and then immunoprecipitated with antibodies against p65/RelA. The ChIP-PCR primers were designed to amplify the proximal promoter regions containing putative NF-κB binding sites within the hsa-miR-125b-1 or hsa-miR-125b-2 promoter as illustrated.

Cell Survival Assay—HEK293 and U2OS cells were mock-transfected or transfected with the indicated plasmids. After 36 h, cells were exposed to UV (20 J/m\(^2\)) alone or in the presence of SB203580 and harvested at various times after UV treatment. Cells were then stained with trypan blue, and the live cell percentage was obtained with a TC10 automated cell counter (Bio-Rad). Data from three independent experiments were pooled and plotted as shown.

Statistical Analysis—The results were presented as mean ± S.D. and analyzed with Student’s t test. \( p < 0.05 \) was denoted as statistically significant.

RESULTS

miRNAs Are Required for UV Radiation-induced Decrease of p38α Expression—In our effort to further explore the cellular stress response to UV radiation, we found that the protein level of p38α, a key UV-responsive kinase, substantially decreased at later time points in human keratinocyte HaCaT cells and HEK293 cells after UV exposure (Fig. 1A and supplemental Fig. 1A). Proteasome inhibitor failed to block the decrease of p38α (supplemental Fig. 1B), suggesting that the mRNA level of p38α may decline upon UV radiation. Indeed, we detected a significant reduction of the p38α mRNA level in both cell lines in response to UV radiation (Fig. 1B). The decrease of the mRNA level may be caused by reduced gene transcription, increased mRNA decay, or both. Intriguingly, we found that the decrease of p38α expression upon UV radiation was remarkably attenuated in Dicer-deficient HCT116 cells compared with wild type cells (Fig. 1C). Dicer is an essential RNase III endonuclease for miRNA biogenesis, and Dicer-disrupted HCT116 cells showed reduced amounts of mature miRNAs and accumulation of

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miRNA precursors when compared with wild type HCT116 cells (26). Therefore, our data suggested that miRNAs may play an important role in this down-regulation of p38α after UV treatment.

Although miRNAs could down-regulate target gene expression via inhibiting protein translation, it was shown that mRNA destabilization usually plays a major role in miRNA-dependent gene repression, especially to those highly repressed targets (16). In accordance with these studies, we found that the mRNA level of p38α upon UV radiation was also significantly lower in wild type HCT116 cells than that in Dicer−/−/− cells (Fig. 1D). To further examine the role of miRNA in UV-induced p38α down-regulation, we generated a luciferase reporter construct in which the luciferase gene was fused with the 3′-UTR of p38α. Interestingly, UV treatment significantly reduced luciferase activity in HEK293 cells expressing this p38α 3′-UTR reporter (Fig. 1E). Moreover, the UV-induced repression of p38α 3′-UTR luciferase activity was abrogated in Dicer−/−/− HCT116 cells (Fig. 1F). These results indicate that the p38α gene 3′-UTR may be subjected to miRNA-dependent repression, resulting in down-regulation of p38α expression in response to UV treatment.

UV Treatment Induces miR-125b Expression—To characterize the miRNAs responsible for p38α down-regulation by UV, we analyzed 3′-UTR of the p38α gene by Targetscan and identified two potential sites complementary to the seed region of the miR-22 or miR-125 family, which are highly conserved across species. We then generated a luciferase reporter that harbors a short fragment of the p38α gene 3′-UTR, including these two miRNA-targeting sites. Interestingly, UV treatment induced a comparable repression of luciferase activity in cells expressing this shorter p38α 3′-UTR reporter and in cells expressing the full-length p38α 3′-UTR reporter, suggesting that the miR-22 and/or miR-125 family may play a major role in regulating p38α expression upon UV radiation (Fig. 1E). In our previous study, we have found that miR-22 expression was significantly increased in cells exposed to UV (27). However, neither overexpression of miR-22 nor inhibiting miR-22 in UV-treated cells affected p38α 3′-UTR reporter activity (data not shown), indicating that miR-22 is unlikely to be a major miRNA responsible for p38α repression upon UV.

We then examined the expression of members of miR-125 family upon UV radiation and found that miR-125b was significantly induced in both HaCaT and HEK293 cells in response to UV exposure (Fig. 2A). Consistently, UV treatment significantly inhibited miR-125b reporter activity, which could be rescued by overexpression of a miR-125b sponge inhibitor (Fig. 2B). Because an increased miRNA level may result from transcriptional up-regulation and/or enhanced post-transcriptional maturation upon DNA damage (14), we further determined the expression of primary miR-125b in UV-treated cells. Interestingly, we found that the primary transcripts from both...
**UV-induced miR-125b Targets p38α**

A schematic representation of the putative miR-125b target site within the 3′-UTR of the p38α gene in different species. The seed region of miR-125b is underlined. A mutant of the p38α 3′-UTR sequence was made as indicated. 

**Figure 3.** miR-125b represses p38α expression via targeting its 3′-UTR. 

A, schematic representation of the putative miR-125b target site within the 3′-UTR of the p38α gene in different species. The seed region of miR-125b is underlined. A mutant of the p38α 3′-UTR sequence was made as indicated. 

B, HEK293 cells were transfected as indicated. After 36 h, cells were treated with UV (20 J/m²), and luciferase activity was quantified at 12 h after treatment. The histogram represents data from three independent experiments, shown as mean ± S.D. (error bars). **, p < 0.01. C, HEK293 cells were transiently transfected with p38α 3′-UTR-WT or Mut reporter, and after 24 h, cells were treated with UV for 12 h or left untreated. Luciferase activity was quantified and analyzed as in B. *, p < 0.05. D, HEK293 cells were either mock-transfected or transfected with increasing amounts (0, 2, or 4 μg) of pre-miR-125b, and whole cell lysates were immunoblotted with p38α and tubulin antibodies. In parallel, relative mRNA levels of p38α in cells transfected with control or pre-miR-125b were analyzed by qRT-PCR. The fold change of relative mRNA expression is shown as mean ± S.D. **, p < 0.01. E, HEK293 cells were either mock-transfected or transfected with miR-125b sponge inhibitor. 36 h later, cells were left untreated or treated with UV and harvested at 12 h after treatment. Whole cell lysates were immunoblotted with p38α and tubulin antibodies. F, HEK293 cells were transfected with plasmids as indicated. Whole cell lysates were subjected to immunoblotting with the indicated antibodies. G, HEK293 cells were either mock-transfected or transfected with HA-p38α. After 36 h, cells were treated with UV (20 J/m²) or left untreated and then harvested at 12 h after treatment. Whole cell lysates were immunoblotted with p38α and tubulin antibodies.

Human miR-125b gene paralogs, *hsa-miR-125b-1* on chromosome 11 and *hsa-miR-125b-2* on chromosome 21, were significantly increased in HaCaT and HEK293 cells upon UV treatment (Fig. 2, C and D). Of note, although the expression of primary miR-125b was maintained at an increased level, the mature form of miR-125b expression had dropped at 12 h after UV treatment. It suggests that UV treatment may inhibit miR-125b processing at later times, which is consistent with a previous report showing that UV could modulate miRNA expression by inducing relocation of miRNA-processing factors Dicer and Ago2 (13). Nevertheless, our data strongly support the notion that UV treatment could induce activation of miR-125b transcription, resulting in increase of the miR-125b level.

**Expression of p38α Is Negatively Regulated by miR-125b**—To determine whether p38α is a gene target of miR-125b, we generated a mutated p38α 3′-UTR luciferase reporter harboring a mutation in the miR-125b target sequence (Fig. 3A). We found that overexpression of miR-125b significantly inhibited luciferase activity in HEK293 cells expressing wild type p38α 3′-UTR reporter but not the mutated 3′-UTR reporter (Fig. 3B). Furthermore, mutation of the miR-125b target sequence also significantly attenuated UV-induced repression of p38α 3′-UTR reporter luciferase activity (Fig. 3C). It is noteworthy that UV-induced inhibition of p38α 3′-UTR reporter activity was still observed even in the presence of miR-125b site mutation, suggesting that other UV-induced miRNAs may also contribute to p38α repression. However, overexpression of miR-125b was sufficient to down-regulate p38α expression at both the protein and mRNA level (Fig. 3D). Accordingly, UV-induced p38α repression was rescued by expressing a miR-125b sponge inhibitor (Fig. 3E). Our data also indicated that 3′-UTR is required for miR-125b-mediated p38α down-regulation because expression of a p38α coding region construct was insensitive to miR-125b overexpression as well as UV radiation (Fig. 3, F and G).

All of this body of evidence indicates that miR-125b plays a critical role in repressing p38α expression through targeting its 3′-UTR upon UV radiation.

**UV-induced NF-κB Activation Is Required for miR-125b Induction**—To delineate the mechanism involved in miR-125b transactivation in response to UV treatment, we examined the impact of various kinase inhibitors on miR-125b induction in UV-treated HaCaT cells. Intriguingly, UV-induced miR-125b up-regulation was significantly inhibited by either ATM inhibitor Ku55933 or IKKβ inhibitor TPCA-1 (Fig. 4A). Our previ-
ous studies have demonstrated that both ATM and IKK are essential kinases required for genotoxic NF-κB signaling (28, 29), so this result indicated a critical role of genotoxic NF-κB signaling in regulating miR-125b transcription upon UV radiation. Consistently, induction of both pri-miR-125b-1 and pri-miR-125b-2 upon UV treatment was remarkably inhibited in the presence of ATM or IKK inhibitor (Fig. 4B). We also observed that UV-induced p38α repression was attenuated by inhibiting either ATM or IKK (Fig. 4, C and D), suggesting that ATM/IKK-dependent NF-κB activation upon UV treatment is required for p38α down-regulation, probably via enhancing miR-125b transcription.

To further investigate the important role of genotoxic NF-κB activation in regulating miR-125b up-regulation in response to UV, we examined miR-125b expression in UV-treated MEF cells. We found that UV treatment induced a substantial increase of miR-125b in wild type MEF cells but not in ATM-deficient MEFs, indicating that ATM is indispensable for miR-125b up-regulation upon UV treatment (Fig. 5A). Moreover, the up-regulation of miR-125b by UV was significantly reduced by overexpressing a dominant negative inhibitor of NF-κB signaling, IκBα superrepressor (S32A/S36A) (Fig. 5, B and C), which was shown to inhibit UV-induced NF-κB activation (7, 10). Accordingly, UV-induced up-regulation of pri-miR-125b-1/-2 transcription was also abrogated in cells expressing IκBα superrepressor (Fig. 5D). These data further support an essential role of the ATM-dependent genotoxic NF-κB activation in regulating miR-125b transcription in response to UV radiation.

To determine whether NF-κB directly regulates miR-125b transcription, we analyzed the upstream sequences of both hsa-miR-125b-1 and -2 and identified two potential NF-κB consensus binding sites in the promoter region of each gene (Fig. 5, F and G, top). Luciferase reporter assay analyses suggested that each potential NF-κB-binding site in either hsa-miR-125b-1 or -2 gene promoters are required for transactivation of the respective gene upon UV treatment (Fig. 5E). Remarkably, we detected significant enrichment of RelA/p65 at respective NF-κB sites (shaded box in Fig. 5, F and G) within promoter regions of both hsa-miR-125b-1 and -2 genes by Chromatin IP analyses, strongly suggesting that NF-κB might activate miR-125b gene transcription via directly binding on its promoter in cells treated by UV (Fig. 5, F and G). Although we did not detect a significant increase of p65 binding on all of the NF-κB sites, data from the luciferase reporter assay indicated that all of these sites were critical for miR-125b gene induction upon UV treatment (Fig. 5E), suggesting that additional members of the NF-κB
family may be recruited to these \( \kappa B \) sites in response to UV treatment. In addition, inhibition of either ATM or IKK\( \beta \) was able to significantly reduce NF-\( \kappa B \)/p65 recruitment to miR-125b gene promoter regions, which further supports the critical role of ATM and IKK\( \beta \) in mediating NF-\( \kappa B \) signaling upon UV radiation.

**ATM Is Indispensable for UV-induced NF-\( \kappa B \) Activation**—It was shown that UV-induced NF-\( \kappa B \) activation required p38\( \alpha \)-dependent CK2 activation (9). We also found that inhibiting either p38\( \alpha \) or CK2 substantially reduced NF-\( \kappa B \) activation in UV-treated HaCaT and HEK293 cells (supplemental Fig. 2A). Besides, our previous studies have demonstrated an essential role of ATM in mediating NF-\( \kappa B \) signaling in response to genotoxic stimulation (25, 28). Interestingly, replication stress inducers, such as hydroxyurea and aphidicolin, also induce NF-\( \kappa B \) activation in an ATM-dependent manner (24). Similar to hydroxyurea and aphidicolin, UV radiation induces a strong replication stress response featured by the quick activation of ATR along with delayed activation of ATM and DNA-PK (1, 30).

We found that both ATM and IKK\( \beta \) appeared to be essential for UV-induced NF-\( \kappa B \) activation in HaCaT and HEK293 cells (Fig. 6A). Consistent with previous reports (7, 10, 11), we found that UV-induced NF-\( \kappa B \) activation was almost abrogated in IKK\( \beta \)-deficient MEFs compared with wild type MEFs (Fig. 6B). Moreover, reconstitution of IKK\( \beta \) dramatically enhanced UV-induced NF-\( \kappa B \) activation in IKK\( \beta \)^{−/−} MEFs.
persistent with our previous studies on replication stress-induced UV treatment may involve the recently reported scaffolding role of IKK—It was shown that p38α inhibition sensitized U2OS cells to UV treatment significantly (Fig. 3F), bypassed the antiapoptotic effect of miR-125b overexpression (Fig. 7A). Accordingly, transfection of miR-125b sponge inhibitor in HaCaT cells significantly enhanced caspase-3 activity and PARP-1 cleavage in response to UV treatment (Fig. 7C). In addition, overexpression of miR-125b sponge inhibitor substantially enhanced and extended p38α activation in cells exposed to UV radiation (Fig. 7, D and E). All of this body of evidence indicates that miR-125b induction antagonizes apoptosis in cells exposed to UV, potentially via prohibiting prolonged hyperactivation of p38α. Consistent with its role in inhibiting caspase activation, up-regulation of miR-125b also substantially enhanced cell survival in response to UV radiation. Overexpression of miR-125b in HEK293 cells significantly improved cell viability after UV radiation, whereas the prosurvival effect was completely blocked by co-transfection of exogenous p38α (Fig. 7F). In line with this observation, U2OS cells overexpressing miR-125b were more resistant to UV-induced cell death, whereas overexpression of miR-125b sponge inhibitor sensitized U2OS cells to UV treatment significantly (Fig. 7G). We also found that inhibiting p38α showed a protective effect set in cells exposed to UV radiation, similar to that in cells overexpressing miR-125b (supplemental Fig. S4, C and D), suggesting that p38α repression may play a major role in miR-125b-dependent protection in cells treated with UV.

**DISCUSSION**

In response to exposure to genotoxic stimuli, such as UV radiation, eukaryotic cells may induce temporary cell cycle arrest and DNA repair to maintain genomic stability. However, if the level of UV-induced DNA damage is too excessive to be

(Fig. 6C). We also found that IKKβ was essential for UV-induced IkBα degradation in MEFs (supplemental Fig. 2B), which may involve the recently reported scaffolding role of IKKβ to facilitate association between IkBα and β-TrCP (11). These data support a critical role of IKKβ in achieving optimal NF-κB activation in cells exposed to UV radiation.

In addition to IKKβ, we found that UV-induced NF-κB activation was abolished in ATM-deficient MEF cells (Fig. 6D). Consistently, inhibiting ATM significantly attenuated NF-κB activation by UV in wild type MEFs (Fig. 6D and supplemental Fig. 2C), whereas reconstitution of ATM in ATM−/− MEFs dramatically increased NF-κB activation in response to UV treatment (Fig. 6E). In addition, ATM knockdown almost abrogated, whereas ATR depletion enhanced, UV-induced NF-κB activation in HEK293 cells (supplemental Fig. 3), which is consistent with our previous studies on replication stress-induced NF-κB activation (24). All of these results strongly suggest that ATM is indispensable for NF-κB activation upon UV radiation. Interestingly, we found that UV-induced p38α activation was substantially inhibited by ATM inhibitor, suggesting that ATM may regulate p38α activation in response to UV treatment (Fig. 6F). Nevertheless, the mechanisms by which ATM regulates p38α activation still remain to be further explored.

**Induction of miR-125b Promotes Cell Survival in Response to UV Treatment**—It was shown that p38α activation promoted apoptosis in cells exposed to UV, which may involve direct phosphorylation and activation of p53 (31, 32). We also found that inhibiting p38α decreased activation of caspase-8 and caspase-3 in cells treated with UV (supplemental Fig. 4A). It is plausible that miR-125b induction may inhibit cell apoptosis via down-regulating p38α in UV-treated cells. Indeed, overexpression of miR-125b inhibited caspase-3/8 activation and PARP1 cleavage in cells exposed to UV (Fig. 7, A and B, and supplemental Fig. 4B). Moreover, co-transfection of a construct containing only the p38α gene coding region, which is insensitive to miR-125b-dependent repression (Fig. 3F), bypassed the antiapoptotic effect of miR-125b overexpression (Fig. 7A). Accordingly, transfection of miR-125b sponge inhibitor in HaCaT cells significantly enhanced caspase-3 activation and PARP-1 cleavage in response to UV treatment (Fig. 7C). In addition, overexpression of miR-125b sponge inhibitor substantially enhanced and extended p38α activation in cells exposed to UV radiation (Fig. 7, D and E). All of this body of evidence indicates that miR-125b induction antagonizes apoptosis in cells exposed to UV, potentially via prohibiting prolonged hyperactivation of p38α. Consistent with its role in inhibiting caspase activation, up-regulation of miR-125b also substantially enhanced cell survival in response to UV radiation. Overexpression of miR-125b in HEK293 cells significantly improved cell viability after UV radiation, whereas the prosurvival effect was completely blocked by co-transfection of exogenous p38α (Fig. 7F). In line with this observation, U2OS cells overexpressing miR-125b were more resistant to UV-induced cell death, whereas overexpression of miR-125b sponge inhibitor sensitized U2OS cells to UV treatment significantly (Fig. 7G). We also found that inhibiting p38α showed a protective effect set in cells exposed to UV radiation, similar to that in cells overexpressing miR-125b (supplemental Fig. S4, C and D), suggesting that p38α repression may play a major role in miR-125b-dependent protection in cells treated with UV.
repaired, cells will undergo apoptosis, which might result from prolonged activation of p38α and p53 (2). Thus, proper control of p38α activation may play a critical role in determining the cell fate between cell survival and apoptotic cell death, which is essential for restoring homeostasis in UV-stressed cells after DNA repair. Therefore, it is not surprising that p53-dependent Wip1 induction, and this served as a negative feedback regulation of p38α activity in cells treated with UV (33).

In this study, we described a novel miR-125b-mediated negative feedback to control p38α activation through post-transcriptional repression of p38α in cells exposed to UV radiation. Intriguingly, the UV-induced expression of miR-125b was regulated by NF-κB, whose activation has been shown to be dependent on p38α. Thus, similar to p53-dependent Wip1 induction, p38α may also induce miR-125b up-regulation via activating NF-κB, which in turn negatively regulates p38α expression to avoid prolonged p38α activation. Besides miR-125b, miR-141 and miR-200a have been shown to target p38α and modulate the oxidative stress response (34). Coincidentally, UV radiation triggers strong oxidative stress, which is one of the major effectors of its genotoxicity. Down-regulation of p38α by miR-141 and miR-200a significantly enhanced cell survival and proliferation of human cancer cells exposed to oxidative stress, further supporting a critical role of p38α in mediating apoptosis, especially under overwhelming stress conditions. We postulate that there are other UV-induced miRNAs involved in regulating p38α expression because overexpression of miR-125b sponge inhibitor was unable to completely block p38α repression. Furthermore, we cannot exclude the possibility that transcriptional inhibition may also contribute to p38α down-regulation after UV radiation. It was shown that the majority of UV-responsive genes were transcriptionally repressed in cells exposed to UV radiation (35), and we also observed a substantial decrease of p38α mRNA in Dicer−/− HCT116 cells after UV treatment, suggesting that the decreased p38α gene transcription may also play a role in p38α down-regulation upon UV treatment. Nevertheless, both protein and mRNA levels of p38α were significantly lower in wild type HCT116 cells than that in Dicer−/− HCT116 cells when exposed to UV, and overexpressing miR-125b significantly increased cell survival upon UV radiation, which was comparable with the effect of p38α inhibition. All of this evidence strongly indicates a pivotal role of miR125b-dependent repression in negatively regulating p38α activity in UV-treated cells.

**FIGURE 7. miR-125b promotes cell survival by repressing p38α.** A, HEK293 cells were transiently transfected with control, pre-miR-125b alone, or pre-miR-125b along with HA-p38α. After 36 h, transfected cells were treated with UV. Whole cell lysates were prepared at the indicated time and immunoblotted as shown. B, U2OS cells were transiently transfected with control or pre-miR-125b, and cells were treated and analyzed as in A. C, HaCaT cells were transfected with control or miR-125b sponge. After 36 h, cells were treated with UV and harvested at 24 h after treatment. Whole cell lysates were immunoblotted with the indicated antibodies. D and E, U2OS (D) or HEK293 (E) cells were transfected and treated with UV as in C and harvested at the indicated times after treatment. Whole cell lysates were analyzed by immunoblotting using the indicated antibodies. F, HEK293 cells were transfected and treated as in A, and the live cell population at indicated times after UV treatment was quantified. The cell survival fraction data from three independent experiments were pooled and are shown as mean ± S.D. (error bars). * p < 0.05. G, U2OS cells were transfected with control, pre-miR-125b, or miR-125b sponge. Cells were treated with UV, and live cell populations were quantified at the time indicated and analyzed as in F. ** p < 0.05.
p38 is a family of MAPks consisting of four isoforms: p38α, p38β, p38γ, and p38δ (36). Both p38α and p38β can be activated by UV exposure; however, their roles in mediating cellular apoptotic response to UV treatment may be distinct. UV-induced p38α activation was shown to promote cell death, whereas p38β may protect cells from UV-induced apoptosis (37). Using TargetScan, we did not find a miR-125b recognition sequence within the 3’-UTR of the p38β gene, suggesting that UV-induced p38α-miR-125b up-regulation may not directly repress p38β expression. However, we cannot rule out the possibility that additional miRNAs may be induced by UV, which could directly target p38β. Because the p38 inhibitor SB203580 inhibits p38α and p38β activity, our data suggest p38α may play a dominant role in determining apoptotic response in cells exposed to UV (supplemental Fig. 1). Nevertheless, selective inhibition of p38α by inhibitors or miRNAs while sparing p38β may further improve cell survival in response to UV treatment.

Previous study implicated that ATM may be involved in regulating NF-κB signaling in UV-treated melanoma cells (38). Using pharmacological and genetic approaches, we demonstrated that ATM is indispensable for NF-κB activation by UV treatment, which is conserved among different cell types and between species. Our data indicated that UV-induced nuclear DNA damage response is involved in mediating NF-κB signaling, even at a relatively early stage (3 h after UV treatment), yet how ATM regulates NF-κB activation upon UV radiation is not entirely clear. Our data indicated that ATM was required for p38α activation by UV. A recent study showed that a cytosolic ATM-NEMO-RIP1 complex mediated p38α activation through recruiting TAK1 in response to genotoxic treatment (39). Our previous studies and others (40, 41) also demonstrated that genotoxic stress may promote ATM nuclear export in association with NEMO, which regulates TAK1 activation in cytoplasm. It is possible that, in response to UV radiation, NEMO may facilitate ATM nuclear export into the cytoplasm, where it mediates TAK1 activation, which in turn activates p38α through phosphorylating MKK3/6. This hypothesis is consistent with the observation that NEMO is required for UV-induced NF-κB activation (7). In parallel, UV radiation was recently shown to induce the nuclear translocation of IkBα and association with IKKβ, which constitutively interacts with β-TrCP through heterogeneous ribonucleoprotein-U, leading to IkBα ubiquitination and degradation (11). Thus, nuclear IKKβ can act as an adaptor protein for IkBα degradation in UV-induced NF-κB activation. We also found that IKKβ was essential for optimal NF-κB activation in response to UV treatment. Because ATM may interact with IKKβ via NEMO association (27), nuclear ATM may also modulate association between IKKβ, IkBα, and heterogeneous ribonucleoprotein-U upon UV radiation. Nonetheless, further investigation is required to examine these hypotheses and explore the mechanistic role of ATM in UV-induced NF-κB signaling.

NF-κB activation is generally considered to be prosurvival. However, UV-induced NF-κB activation has also been shown to actively repress transcription of antiapoptotic genes, such as XIAP and BCL2L1, which may promote cell death (42). We found that UV-induced NF-κB activation was required for up-regulation of miR-125b, which promoted cell survival via repressing p38α. NF-κB was also considered as one of the major contributors in the oncogenesis of UV-induced skin cancers, probably through up-regulating its prosurvival target genes, such as COX-2 and BCL2 (43). Therefore, the impact of NF-κB activation on cell survival and proliferation in response to UV probably needs to be weighed in the context of cell types and the dose and wavelength of UV as well as its extent and duration. Similarly, the roles of miR-125b in regulating cell growth and tumor progression are being actively studied but remain inconclusive. Increased expression of miR-125b has been observed in a variety of hematopoietic malignancies, including acute myeloid leukemia, myelodysplastic syndrome, and acute lymphoblastic leukemia (44). The oncogenic function of miR-125b was associated with reduction of proapoptotic genes, such as BAK1, TP53, and PUMA, or skewing hematopoietic lineage differentiation via repressing Lin28A (45). The roles of miR-125b in solid tumors are relatively controversial. Overexpression of miR-125b was found in prostate cancer and glioma patient samples (46, 47). Up-regulation of the miR-125 family was also associated with increased cancer metastasis (48). However, it was found that miR-125b could down-regulate certain onco-genes, such as MUC1, ERBB2, and ERBB3, resulting in growth inhibition and enhanced sensitivity to genotoxic anti-cancer agents in breast cancer cells (49, 50). In contrast, miR-125b was found to be up-regulated in Taxol-resistant cancer cells, which may inhibit Taxol-induced apoptosis and confer therapeutic resistance in breast cancer cells (51). All of these findings further underlined the notion that miRNAs can function as either oncogenes or tumor suppressors, depending on the genes they target in the context of different cancers (52).

Contradictory data regarding the NF-κB-dependent regulation of miR-125b transcription have been reported. The NF-κB activation has been shown to both transactivate and repress miR-125b expression in immune response elicited by LPS (21, 53). Here we found that UV-induced NF-κB activation was required for miR-125b transactivation, suggesting that NF-κB may exert a distinct role in regulating miR-125b expression, depending on cell types and stimuli. Nevertheless, in skin cells exposed to UV radiation, NF-κB probably plays an oncogenic role through promoting miR-125b-dependent p38α repression.

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