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UV-induced interaction between p38 MAPK and p53 serves as a molecular switch in determining cell fate

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ABSTRACT

p53 plays a fundamental role in the maintenance of genome integrity after DNA damage, deciding whether cells repair and live, or die. However, the rules that govern its choice are largely undiscovered. Here we show that the functional relationship between p38 and p53 is crucial in defining the cell fate after DNA damage. Upon low dose ultraviolet (UV) radiation, p38 and p53 protect the cells from apoptosis separately. Conversely, they function together to favor apoptosis upon high dose UV exposure. Taken together, a UV-induced, dose-dependent interaction between p38 and p53 acts as a switch to determine cell fate.

Structured summary:
MINT-8050838: *p53* (uniprotkb:P02340) *physically interacts* (MI:0915) with *p38* (uniprotkb:P47811) by *anti bait coimmunoprecipitation* (MI:0006)
MINT-8050948: *p53* (uniprotkb:P04637) *physically interacts* (MI:0915) with *p38* (uniprotkb:P47811) by *anti tag coimmunoprecipitation* (MI:0007)

1. Introduction

The cellular responses to injuries or stresses are important in determining cell fate [1]. Many signaling pathways participate in this process, with the mitogen-activated protein kinase (MAPK) cascades and p53 pathway two of the major pathways implicated [1–3].

p38 MAPK, one of the four MAPK subfamilies in mammalian cells, is activated by proinflammatory cytokines and environmental stresses [4–6]. p38 is not only reported to be phosphorylated and activated to mediate cell apoptosis [7–9], but also to have cell protective effects under certain circumstances [10,11]. Why p38 has opposing functions in determining cell fate in different situations remains unclear.

p53 is one of the most intensively studied tumor suppressor proteins. In response to DNA damage, the activation of p53 leads to cell cycle arrest, DNA repair, or apoptosis [1,12,13]. Understanding the rules that govern p53's choice is of fundamental importance, especially in our battle against cancer. However, it is largely unknown how the decisions are made upstream of p53 [1,3,14].

Several studies have shown functional links between p38 and p53 in the regulation of apoptosis and that phosphorylation and activation of p53 by p38 may lead to different outcomes under different conditions [8,10]. Hence, it is of great necessity to clarify their roles in the determination of cell fate.

In this report, *p38* or *p53* gene knockout cell lines are employed to study their roles in cell fate decisions upon different doses of ultraviolet (UV) radiation. Based on our findings, we propose that the interaction between p38 and p53 serves as a dose-dependent molecular switch to mediate cell survival or apoptosis, providing a novel mechanism for their functional links in response to cellular stresses.

2. Materials and methods

2.1. Plasmids

cDNA encoding human p53 was subcloned by PCR into a revised pcDNA3 vector which carried an HA tag. The Ser15 mutant of p53, p53 (S15A), was mutated from wild-type p53 (p53 (WT)) with MutanBEST mutagenesis kit (TaKaRa). The recombinant clones were identified by sequencing. FLAG-p38 was constructed as described in [4].

Abbreviations: UV, ultraviolet; MAPK, mitogen-activated protein kinase; MEF, mouse embryonic fibroblast; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; ATM/ATR, ataxia telangiectasia mutated/ataxia telangiectasia related; HIPK2, homeodomain-interacting protein kinase 2

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2.2. Cell culture and transfection

Wild-type mouse embryonic fibroblasts (MEFs) (C57B1/6 background), $p38^{+/+}$, $p38^{-/-}$, $p53^{+/+}$ and $p53^{-/-}$ MEFs, as well as NIH3T3 cells, were maintained in Dulbecco's Modified Eagle Medium (DMEM, GIBCO BRL/Invitrogen) supplemented with 5% fetal bovine serum (FBS, Hyclone) in the cell incubator (37 °C, 5% CO_2). NIH3T3 cells were transfected with Polyfect (Qiagen) following the guide of the manufacturer's protocol.

2.3. UV radiation

The UVC (254 nm) radiation was performed with a UV light meter (Model YK-34UV, Lutron Electronic). 10 or 30 J/m^2 UV radiations were defined as low or high doses for MEFs, respectively, and 5 or 20 J/m^2 radiations were defined as those for NIH3T3 cells, respectively.

2.4. Immunoblotting

Immunoblotting analyses were performed as previously described [15]. The antibodies of p53 (#2524), p-p53 (Ser15) (#9284), p38 (#9228), p-p38 (#9211), extracellular signal-regulated kinase (ERK) (#9102), p-ERK (#9101), HA (#2362), β-actin (#4967), and phospho-p53 antibody sampler kit (#9919) were purchased from Cell Signaling Technology. Anti-FLAG antibody (200472) was obtained from Stratagene.

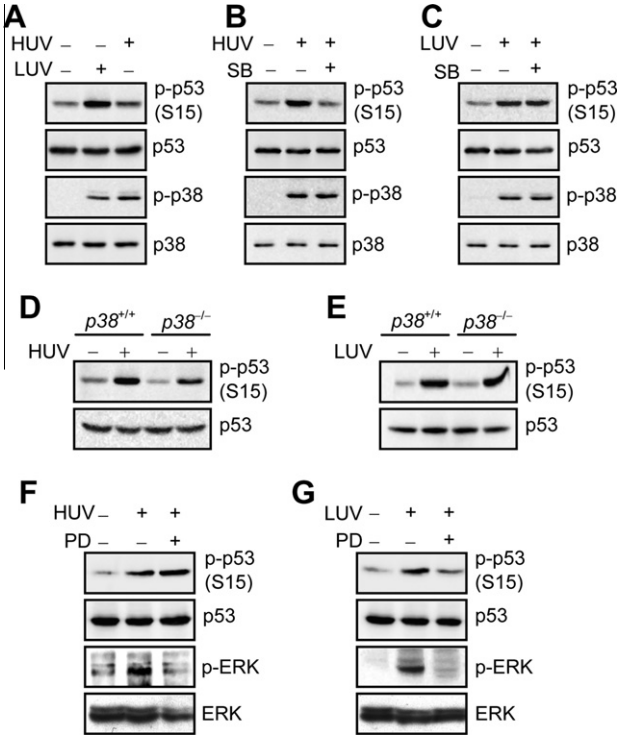

Fig. 1. Dose-dependent Ser15 phosphorylation of p53 by p38 or ERK upon UV radiation. (A) MEFs were treated with either 30 J/m^2 (HUV) or 10 J/m^2 (LUV) UV for 1 h, and the phosphorylation levels of p53 and p38 were detected. (B and C) MEFs were pretreated with DMSO or SB203580 (SB, 20 μM) for 30 min, followed by either not treated or treated with HUV (B) or LUV (C) for 1 h, and the phosphorylation levels of p53 and p38 were detected. (D and E) $p38^{+/+}$ and $p38^{-/-}$ cells were either not treated or treated with HUV (D) or LUV (E) for 1 h, and the phosphorylation levels of p53 and p38 were detected. (F and G) MEFs were pretreated with DMSO or PD98059 (PD, 20 μM) for 30 min, followed by either not treated or treated with HUV (F) or LUV (G) for 1 h, and the phosphorylation levels of p53 and ERK were detected.

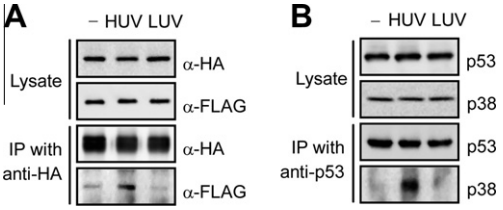

Fig. 2. UV-induced, dose-dependent interaction between p38 and p53. (A) NIH3T3 cells were co-transfected with FLAG-p38 and HA-p53 and were either not treated or treated with HUV or LUV for 1 h. The cell lysates and immunoprecipitates were detected by immunoblotting with HA or FLAG antibodies. (B) MEFs were treated as in (A). The cell lysates and immunoprecipitates were detected with p53 or p38 antibodies.

2.5. Apoptosis assay

Apoptosis analysis was performed with an Annexin V-FITC apoptosis detection kit (Biovision). In brief, the cells were treated, trypsinized and counted, then 1×10^6 cells were stained in dark with 50 μg/ml Annexin V-FITC at room temperature for 5 min and 100 μg/ml propidium iodide (PI) at 4 °C for 5 min in turn. Doubly stained cells were promptly analyzed by a FACS Calibur (Becton-Dickinson) flow cytometer. Annexin V-positive, PI-negative cells were counted as apoptotic cells.

2.6. Co-immunoprecipitation and statistical analysis

Experimental details are presented in Supplementary data.

3. Results

3.1. UV-induced p53 phosphorylation on Ser15 by p38 is dose-dependent

To explore the effects of different doses of UV radiation on p38 and p53, MEFs were irradiated with either 30 J/m^2 (high dose UV, HUV) or 10 J/m^2 (low dose UV, LUV) UV [12,16]. HUV and LUV-induced phosphorylation of p53 on Ser15, a widely reported phosphorylation site of p53 by p38 upon UV radiation [6,17], were different. Surprisingly, LUV induced a higher level of phosphorylation on p53 Ser15 than HUV (Fig. 1A).

p38 specific inhibitor SB203580 only blocked HUV-induced Ser15 phosphorylation (Fig. 1B and C), suggesting that HUV, but not LUV-induced Ser15 phosphorylation is mediated by p38. This conclusion was further confirmed with *p38* gene knockout cells (Fig. 1D and E). The residual activity may be due to another p38 subfamily member, p38β. On the contrary, PD98059, an ERK pathway inhibitor, only blocked LUV-induced Ser15 phosphorylation (Fig. 1F and G), demonstrating its role in p53 regulation under LUV condition.

3.2. Dose-dependent interaction between p38 and p53 induced by UV radiation

To determine the interaction between p38 and p53 upon HUV or LUV radiation, co-immunoprecipitation experiments were performed. As shown in Fig. 2A and B, p38 was only co-precipitated by p53 with HUV radiation. Although there already existed reports regarding UV-induced interaction between p38 and p53 [6,8], our results clarified that this interaction was only induced by HUV, but not LUV radiation.

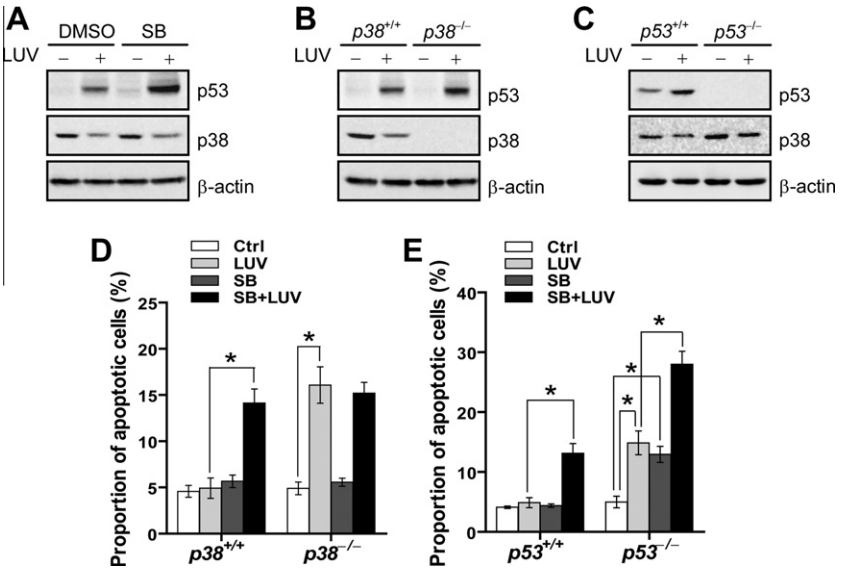

Fig. 3. Effects of *p38* or *p53* gene knockout on cell apoptosis induced by low dose UV radiation. (A) MEFs were pretreated with DMSO or SB203580 (SB, 20 μM) for 30 min, and treated with or without 10 J/m^2 UV (LUV) for 6 h. The expression levels of p53 and p38 were detected. (B) $p38^{+/+}$ and $p38^{-/-}$ cells were treated with or without LUV for 6 h, and the expression levels of p53 and p38 were detected. (C) $p53^{+/+}$ and $p53^{-/-}$ cells were treated with or without LUV for 6 h, and the expression levels of p53 and p38 were detected. (D) $p38^{+/+}$ and $p38^{-/-}$ cells were treated with or without LUV for 6 h, and the proportions of apoptotic cells were analyzed. *$P < 0.01$. (E) $p53^{+/+}$ and $p53^{-/-}$ cells were treated with or without LUV for 6 h, and the proportions of apoptotic cells were analyzed. *$P < 0.01$.

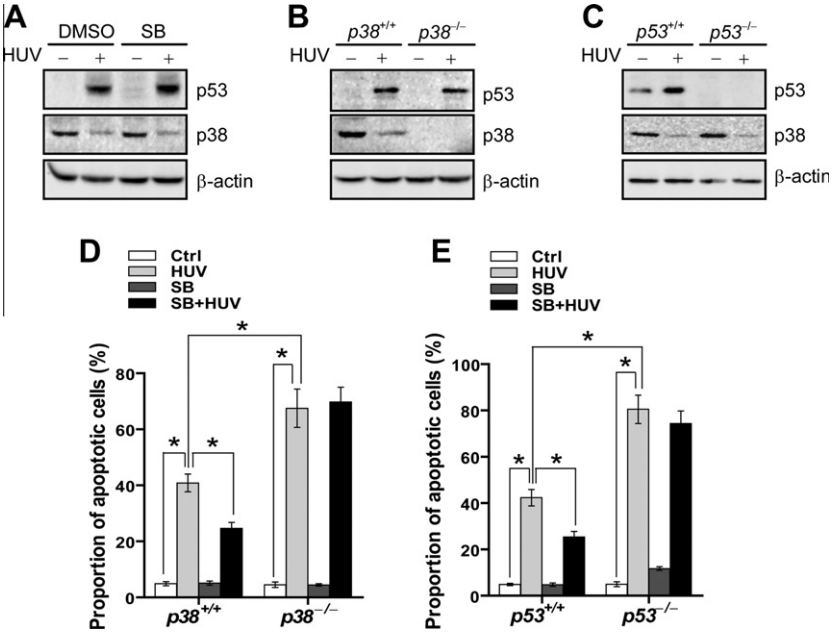

Fig. 4. Effects of *p38* or *p53* gene knockout on cell apoptosis induced by high dose UV radiation. (A) MEFs were pretreated with DMSO or SB203580 (SB, 20 μM) for 30 min, and treated with or without 30 J/m^2 UV (HUV) for 6 h. The expression levels of p53 and p38 were detected. (B) $p38^{+/+}$ and $p38^{-/-}$ cells were treated with or without HUV for 6 h, and the expression levels of p53 and p38 were detected. (C) $p53^{+/+}$ and $p53^{-/-}$ cells were treated with or without HUV for 6 h, and the expression levels of p53 and p38 were detected. (D) $p38^{+/+}$ and $p38^{-/-}$ cells were treated with or without HUV for 6 h, and the proportions of apoptotic cells were analyzed. *$P < 0.01$. (E) $p53^{+/+}$ and $p53^{-/-}$ cells were treated with or without HUV for 6 h, and the proportions of apoptotic cells were analyzed. *$P < 0.01$.

3.3. Anti-apoptotic effects of p38 and p53 upon LUV radiation

It has been shown that p53 accumulates upon UV radiation [12,13,17]. p53 was greatly up-regulated 6 h after LUV radiation, while the p38 level decreased (Fig. 3A). SB203580 pretreatment made p53 accumulation reach an even higher level than LUV radiation alone. Consistently, p53 accumulation in $p38^{-/-}$ cells was also higher than that in $p38^{+/+}$ cells with LUV radiation (Fig. 3B). On the other hand, the expression levels of p38 in $p53^{-/-}$ cells with or without LUV radiation were both higher than those in $p53^{+/+}$ cells, respectively (Fig. 3C). These results suggested that these two proteins might have coordinate effects on cell responses upon LUV radiation, as p38 inhibition led to a higher level of p53 to possibly compensate for loss of p38 function, and vice verse.

We further studied the effects of *p38* or *p53* gene knockout on LUV-induced cell apoptosis. It was shown that SB203580 pretreatment significantly increased LUV-induced apoptosis of

$p38^{+/+}$ cells, while the proportion of apoptotic $p38^{-/-}$ cells induced by LUV significantly increased in comparison with that of the untreated cells. No difference was observed in $p38^{+/+}$ cells (Fig. 3D). Meanwhile, the apoptotic proportion of $p53^{-/-}$ cells treated with LUV also significantly increased compared with that of the untreated cells (Fig. 3E). Interestingly, SB203580 pretreatment alone significantly increased the apoptosis of resting $p53^{-/-}$ cells and SB203580 pretreatment followed by LUV radiation elevated further the proportion of apoptotic $p53^{-/-}$ cells, suggesting p38 and p53 have separate protective effects on LUV-induced apoptosis.

3.4. Pro-apoptotic effects of p38 and p53 upon HUV radiation

Unlike LUV, inhibition of either p38 or p53 had no effect on the expression level of the other upon HUV radiation (Fig. 4A–C). Moreover, HUV radiation induced a significant increase in apoptotic $p38^{+/+}$ cells. SB203580 pretreatment inhibited this increase in apoptosis, suggesting p38 plays a role in HUV-induced apoptosis. Surprisingly, a higher level of apoptosis was induced by HUV in $p38^{-/-}$ cells than that in $p38^{+/+}$ cells (Fig. 4D). For $p53^{+/+}$ and $p53^{-/-}$ cells, HUV-induced effects were similar to those in $p38^{+/+}$ and $p38^{-/-}$ cells (Fig. 4E). These results suggested that although p38 and p53 mediated HUV-induced apoptosis, they were also essential for cells to endure stresses. One reason why the results from SB203580 pretreatment and from the *p38* knockout cell line were different may be that p38β in $p38^{-/-}$ cells can still mediate the apoptosis upon HUV radiation. As SB203580 pretreatment had no effect on HUV-induced apoptosis in $p53^{-/-}$ cells (Fig. 4E), the activation of p38 and p53 should be part of the same signaling event in this process.

3.5. Ser15 of p53 is the key phosphorylation site in determining cell fate after UV radiation

We further investigated the exact role of Ser15 in LUV or HUV-induced apoptosis. The expression of p53 (S15A) significantly decreased HUV-induced apoptosis compared to p53 (WT) expression (Fig. 5A and B), suggesting that phosphorylation on Ser15 of p53 plays a key role in HUV, but not LUV-induced apoptosis.

4. Discussion

p53 plays an essential role in the maintenance of genome integrity after DNA damage [1,14]. The damaged cell is confronted with a choice: repair and live, or die. This process is basically decided by p53, largely through different post-translational modifications and specific induction of its target genes [1,3,18]. Several studies have thrown light on the notion that different doses or wavelengths of UV radiation may bring about different cell fates [14,19–21], yet a gap in our understanding on how different UV doses lead to different modifications of p53 still exists.

UVC radiation (20–50 J/m^2) are most commonly used for inducing apoptosis [8,12,16]. In our study, we selected 10 and 30 J/m^2 UVC as low and high dose radiation, respectively. It was shown that *p38*- or *p53*-deficient cells were more sensitive to both LUV and HUV-induced apoptosis than wild-type cells, suggesting they are essential for the cellular endurance to stresses, no matter mild or intensive, and cells lacking either of them are more susceptible to apoptosis. The cellular protective effects of p38 and p53 which have been previously reported, may be due to their functions in cell cycle arrest and DNA repair [9,22,23]. Remarkable differences

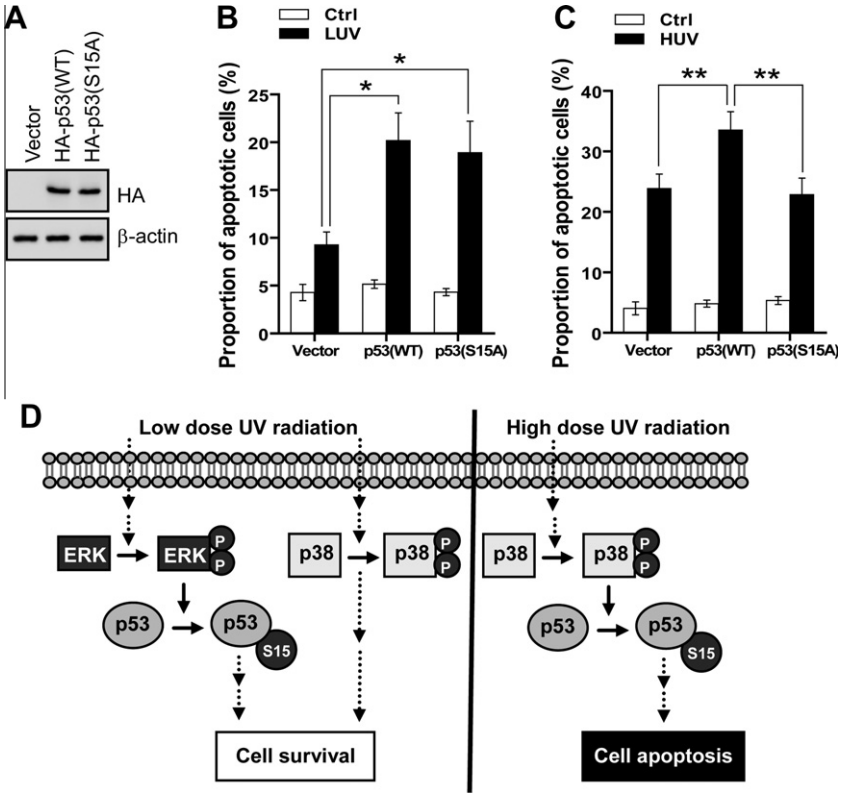

Fig. 5. Role of Ser15 of p53 on cell apoptosis induced by UV radiation. (A) The expression of HA-tagged p53 (WT) and p53 (S15A) in NIH3T3 cells. (B) NIH3T3 cells were transfected with different vectors and treated with or without 5 J/m^2 UV (LUV) for 6 h. The proportions of apoptotic cells were analyzed. $^*P < 0.01$. (C) NIH3T3 cells were transfected and treated with or without 20 J/m^2 UV (HUV) for 6 h, and the proportions of apoptotic cells were analyzed. $^{**}P < 0.05$. (D) A model for the interaction between p38 and p53 serving as a molecular switch to control cell survival/death responses induced by UV radiation.

between LUV and HUV-induced cell responses were observed. In wild-type cells, LUV induced p38 and p53 activation and promoted survival, while their activations upon HUV radiation led to apoptosis, reflecting their roles in cell fate decisions. The results with SB203580 pretreatment further indicated that their protective effects upon LUV radiation were separate, whereas their roles in HUV-induced apoptosis were interdependent.

UV-induced phosphorylation of p53 is mediated by a variety of protein kinases, including p38, ERK, c-Jun N-terminal kinase (JNK), homeodomain-interacting protein kinase 2 (HIPK2), and ataxia telangiectasia mutated/ataxia telangiectasia related (ATM/ATR) [6,8,17,22,24]. Upon UV radiation, p38 phosphorylates p53 on at least four sites (Ser15, Ser33, Ser46, and Ser392), leading to its escape from Mdm2-dependent degradation [6,8,12,17,25]. However, among all the phosphorylation sites we detected, including Ser6, Ser9, Ser15, Ser20, Ser37, Ser46, and Ser392 (Fig. S1), only Ser15 showed significant dose-dependent phosphorylation in our model. Ser15 phosphorylation is critical for the stabilization, nuclear localization and functional activation of p53 [2,6,26]. UV-induced Ser15 phosphorylation is also mediated by ERK and ATM/ATR (for ATM/ATR, only upon very low doses of UV radiation) [6,17]. JNK, another MAPK family member, only phosphorylates p53 on Ser20 upon UV radiation [17]. Although Ser15 was reported to be phosphorylated by p38 and ERK simultaneously [6], our study showed that HUV and LUV-induced Ser15 phosphorylation was mediated by p38 and ERK, respectively. This suggests that p53-mediated determination of cell fate is regulated by different upstream kinases. The report by Latonen et al. which showed different results from ours, may be because they detected the phosphorylation levels at 6 h after radiation compared to our 1 h [12]. This speculation was confirmed by the detection of Ser15 phosphorylation 6 h after treatment (Fig. S2). The interaction data between p38 and p53 was consistent with the activation results as interaction only occurred upon HUV radiation. Different effects of p53 (WT) and p53 (S15A) on HUV or LUV-induced apoptosis further verified the key role of Ser15 in the cell fate decision drawn by the dose-dependent interaction between p38 and p53.

Based on our findings, we propose a model in which UV-induced interaction between p38 and p53 serves as a molecular switch for determining cell fate (Fig. 5D). When the cells are irradiated with LUV and the injuries are reparable, p38 and p53 are activated separately, contributing to the initiation of internal repair mechanisms, resulting in cell survival. Accumulation of p53 induces the transcription of $p21^{Waf1/Cip1}$, which arrests cell cycle progression by inhibiting cyclin-dependent kinases (CDKs) [12,13]. The survival-promoting effect of p38 may be achieved through its activation of MK2, which in turn activates Cdc25A/B-mediated G1/S and G2/M arrests [22,25,27]. On the contrary, when the cells are irradiated with HUV causing irreparable injuries, activated p38 directly binds to and phosphorylates p53 on Ser15, leading to cell apoptosis. p53 promotes apoptosis through its regulation of Bcl-2 family members, and the induction of Gadd45 and p53 inducible genes [12,14]. Through these intracellular mechanisms, the cells precisely sense the intensities of the stresses and make a suitable decision on their own fate.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.febslet.2010.10.057.

References

[1] Aylon, Y. and Oren, M. (2007) Living with p53, dying of p53. Cell 130, 597–600.
[2] Brown, L. and Benchimol, S. (2006) The involvement of MAPK signaling pathways in determining the cellular response to p53 activation: cell cycle arrest or apoptosis. J. Biol. Chem. 281, 3832–3840.
[3] Li, Q. et al. (2009) Axin determines cell fate by controlling the p53 activation threshold after DNA damage. Nat. Cell Biol. 11, 1128–1134.
[4] Jiang, Y., Chen, C., Li, Z., Guo, W., Gegner, J.A., Lin, S. and Han, J. (1996) Characterization of the structure and function of a new mitogen-activated protein kinase (p38beta). J. Biol. Chem. 271, 17920–17926.
[5] Johnson, G.L. and Lapadat, R. (2002) Mitogen-activated protein kinase pathways mediated by ERK, JNK, and p38 protein kinases. Science 298, 1911–1912.
[6] She, Q.B., Chen, N. and Dong, Z. (2000) ERKs and p38 kinase phosphorylate p53 protein at serine 15 in response to UV radiation. J. Biol. Chem. 275, 20444–20449.
[7] Bulavin, D.V. and Fornace Jr., A.J. (2004) P38 MAP kinase's emerging role as a tumor suppressor. Adv. Cancer Res. 92, 95–118.
[8] Bulavin, D.V., Saito, S., Hollander, M.C., Sakaguchi, K., Anderson, C.W., Appella, E. and Fornace Jr., A.J. (1999) Phosphorylation of human p53 by p38 kinase coordinates N-terminal phosphorylation and apoptosis in response to UV radiation. EMBO J. 18, 6845–6854.
[9] Porras, A., Zuluaga, S., Black, E., Valladares, A., Alvarez, A.M., Ambrosino, C., Benito, M. and Nebreda, A.R. (2004) P38 alpha mitogen-activated protein kinase sensitizes cells to apoptosis induced by different stimuli. Mol. Biol. Cell 15, 922–933.
[10] Chouinard, N., Valerie, K., Rouabhia, M. and Huot, J. (2002) UVB-mediated activation of p38 mitogen-activated protein kinase enhances resistance of normal human keratinocytes to apoptosis by stabilizing cytoplasmic p53. Biochem. J. 365, 133–145.
[11] Park, J.M., Greten, F.R., Li, Z.W. and Karin, M. (2002) Macrophage apoptosis by anthrax lethal factor through p38 MAP kinase inhibition. Science 297, 2048–2051.
[12] Latonen, L., Taya, Y. and Laiho, M. (2001) UV-radiation induces dose-dependent regulation of p53 response and modulates p53-HDM2 interaction in human fibroblasts. Oncogene 20, 6784–6793.
[13] Shaulian, E., Schreiber, M., Piu, F., Beeche, M., Wagner, E.F. and Karin, M. (2000) The mammalian UV response: c-Jun induction is required for exit from p53-imposed growth arrest. Cell 103, 897–907.
[14] Knezevic, D., Zhang, W., Rochette, P.J. and Brash, D.E. (2007) Bcl-2 is the target of a UV-inducible apoptosis switch and a node for UV signaling. Proc. Natl. Acad. Sci. USA 104, 11286–11291.
[15] Gong, X., Ming, X., Deng, P. and Jiang, Y. (2010) Mechanisms regulating the nuclear translocation of p38 MAP kinase. J. Cell. Biochem. 110, 1420–1429.
[16] Takekawa, M., Adachi, M., Nakahata, A., Nakayama, I., Itoh, F., Tsukuda, H., Taya, Y. and Imai, K. (2000) P53-inducible wip1 phosphatase mediates a negative feedback regulation of p38 MAPK-p53 signaling in response to UV radiation. EMBO J. 19, 6517–6526.
[17] Wu, G.S. (2004) The functional interactions between the p53 and MAPK signaling pathways. Cancer Biol. Ther. 3, 156–161.
[18] Das, S., Raj, L., Zhao, B., Kimura, Y., Bernstein, A., Aaronson, S.A. and Lee, S.W. (2007) Hzf Determines cell survival upon genotoxic stress by modulating p53 transactivation. Cell 130, 624–637.
[19] Cuadrado, A., Lafarga, V., Cheung, P.C., Dolado, I., Llanos, S., Cohen, P. and Nebreda, A.R. (2007) A new p38 MAP kinase-regulated transcriptional coactivator that stimulates p53-dependent apoptosis. EMBO J. 26, 2115–2126.
[20] Li, G. and Ho, V.C. (1998) P53-dependent DNA repair and apoptosis respond differently to high- and low-dose ultraviolet radiation. Br. J. Dermatol. 139, 3–10.
[21] Mathonnet, G., Leger, C., Desnoyers, J., Drouin, R., Therrien, J.P. and Drobetsky, E.A. (2003) UV wavelength-dependent regulation of transcription-coupled nucleotide excision repair in p53-deficient human cells. Proc. Natl. Acad. Sci. USA 100, 7219–7224.
[22] Reinhardt, H.C., Aslanian, A.S., Lees, J.A. and Yaffe, M.B. (2007) P53-deficient cells rely on ATM- and ATR-mediated checkpoint signaling through the p38MAPK/MK2 pathway for survival after DNA damage. Cancer Cell 11, 175–189.
[23] Tomicic, M.T., Christmann, M. and Kaina, B. (2005) Apoptosis in UV-C light irradiated p53 wild-type, apaf-1 and p53 knockout mouse embryonic fibroblasts: interplay of receptor and mitochondrial pathway. Apoptosis 10, 1295–1304.

[24] Hofmann, T.G., Möller, A., Sirma, H., Zentgraf, H., Taya, Y., Dröge, W., Will, H. and Schmitz, M.L. (2002) Regulation of p53 activity by its interaction with homeodomain-interacting protein kinase-2. Nat. Cell Biol. 4, 1–10.
[25] Weber, H.O., Ludwig, R.L., Morrison, D., Kotlyarov, A., Gaestel, M. and Vousden, K.H. (2005) HDM2 phosphorylation by MAPKAP kinase 2. Oncogene 24, 1965–1972.
[26] Bean, L.J. and Stark, G.R. (2001) Phosphorylation of serines 15 and 37 is necessary for efficient accumulation of p53 following irradiation with UV. Oncogene 20, 1076–1084.
[27] Lemaire, M., Ducommun, B. and Nebreda, A.R. (2010) UV-induced downregulation of the CDC25B protein in human cells. FEBS Lett. 584, 1199–1204.