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MST1 activation by curcumin mediates JNK activation, Foxo3a nuclear translocation and apoptosis in melanoma cells

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ABSTRACT

Different groups including ours have shown that curcumin induces melanoma cell apoptosis, here we focused the role of mammalian Sterile 20-like kinase 1 (MST1) in it. We observed that curcumin activated MST1-dependent apoptosis in cultured melanoma cells. MST1 silencing by RNA interference (RNAi) suppressed curcumin-induced cell apoptosis, while MST1 over-expressing increased curcumin sensitivity. Meanwhile, curcumin induced reactive oxygen species (ROS) production in melanoma cells, and the ROS scavenger, N-acetyl-cysteine (NAC), almost blocked MST1 activation to suggest that ROS might be required for MST1 activation by curcumin. c-Jun N-terminal protein kinase (JNK) activation by curcumin was dependent on MST1, since MST1 inhibition by RNAi or NAC largely inhibited curcumin-induced JNK activation. Further, curcumin induced Foxo3 nuclear translocation and Bim-1 (Foxo3 target gene) expression in melanoma cells, such an effect by curcumin was inhibited by MST1 RNAi. In conclusion, we suggested that MST1 activation by curcumin mediates JNK activation, Foxo3a nuclear translocation and apoptosis in melanoma cells.

1. Introduction

The incidence of malignant melanoma increases over the last 30 years in Caucasians, and it continues to be one of the leading causes of cancer-related deaths in the US and around the world [1,2]. Due to the fact that malignant melanoma cells are generally less response to traditional chemo-drugs [3–5], long-term survival of metastatic melanoma patients is dismal [1,3–5].

Curcumin, 1,7-bis(4-hydroxy-3methoxyphenyl)-1,6-heptadien-3,5-dione, is the primary bioactive component of turmeric, the dietary spice made from the rhizome of Curcuma longa [6]. It possesses wide-range anti-tumor properties [6], which are mainly attributed to its abilities to induce cancer cell apoptosis, and to inhibit cancer-related angiogenesis and/or inflammations [6]. Preclinical studies (including ours [7,8]) have confirmed that curcumin's dramatic anti-melanoma efficiency both *in vivo* and *in vitro* [6,9–11]. Several phase I and phase II clinical trials indicate that curcumin is quite safe and may exhibit therapeutic efficacy in patients with melanoma [9].

The underlying mechanisms of curcumin-induced tumor cell apoptosis remain to be explored [6,12]. It has been shown that curcumin induces tumor cell growth inhibition and apoptosis through regulation of multiple signaling pathways, including cell proliferation/survival pathways, apoptosis pathways, tumor suppressor pathway, and multiple protein kinase pathways [12]. Our previous studies have been focusing on how curcumin kills melanoma cells, and several mechanisms including c-Jun N-terminal protein kinase (JNK) activation [7], ceramide and reactive oxygen species (ROS) production [8,9,11] have been proposed.

MST1 (mammalian STE20-like kinase 1) is a serine/threonine kinase that is activated during apoptosis [13–15], which in turn activates its downstream pro-apoptotic targets including JNK, histone H2B and Foxo [13–15]. A number of stress inducers including chemo-drugs activates MST1-dependent cell apoptosis [16]. In the current study, we found that curcumin-induced melanoma cell apoptosis was also dependent on MST1 activation.

2. Materials and methods

2.1. Chemicals and reagents

N-acetyl-cysteine (NAC), antibodies of MST1 and Foxo3a were purchased from Santa Cruz Biotechnology (Santa Cruz, CA).

Abbreviations: MST1, mammalian Sterile 20-like kinase 1; JNK, c-Jun N-terminal protein kinase; NAC, N-acetyl-cysteine; ROS, reactive oxygen species; IP, immunoprecipitation; RNAi, RNA interference; MTT, 3-(4,5-dimethyl-thiazol-2-yl)2,5-diphenyl tetrazolium bromide.

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Curcumin and mouse monoclonal anti-tubulin antibody were obtained from Sigma (St. Louis, MO). Antibodies of phospho-MST1 (Thr 183), JNK1, c-Jun, phospho-JNK1/2 (Thr 183/Tyr 185), Bim-1, cleaved-caspase 3 and cleaved-caspase 9 were purchased from Cell Signaling Technology (Bevery, MA).

2.2. Cell culture

Melanoma cell lines B16 and WM-115 [7,8], as well as HEK-293 cells were maintained in a DMEM medium, supplemented with a 10% FBS (Sigma, St. Louis, MO), Penicillin/Streptomycin (1:100, Sigma) and 4 mmol/L L-glutamine (Sigma, St. Louis, MO), in a CO_2 incubator at 37 °C .

2.3. Cell survival assay

Cell survival was measured by 3-(4,5-dimethyl-thiazol-2-yl)2,5-diphenyl tetrazolium bromide (MTT) dye assay as described [7,8]. Value of treatment group was expressed as percentage change vs. untreated control group.

2.4. Apoptosis assay

After treatment, melanoma cells were washed with cold PBS and incubated with 0.5 ml of Binding Buffer (10 mM HEPES, pH 7.4, 150 NaCl, 2.5 $CaCl_2$, and 1 mM $MgCl_2$, and 4% BSA), containing 3 μg/ml annexin V-FITC for 10 min. Cells were then washed with PBS and resuspended. A total of 20,000 cells of each sample were analyzed by flow cytometry in a FACS (Beckton Dickinson FACScan, Taibei, China). The percentage of Annexin V was recorded as apoptosis rate.

2.5. Reactive oxygen species (ROS) assay

ROS level was determined by concomitant increase in dichlorofluorescein fluorescence (DCFH-DA), according to protocol (Gene Research Lab, Taibei, China), as previous reported [17]. After indicated treatments, melanoma cells were stained with 10 μM of DCFH-DA for 30 min at 37 °C. Fluorescently stained cells were transferred to polystyrene tubes with cell-strainer caps (Falcon, Shanghai, China) and subjected to FACS, using Cell Quest 3.2 (Beckton Dickinson) software for acquisition and analysis. In each analysis, 20,000 events were recorded. Induction of ROS generation was expressed in arbitrary units (vs. Control).

2.6. Immunoblotting

Immunoblotting was performed according to previous protocol [7,8]. For detecting nuclear proteins, nuclear fractions of attached cells were isolated based on protocols of [18]. The band intensity was quantified through ImageJ software. The intensity of each phosphorylated kinase was normalized to the intensity of non-phosphorylated kinase. The value was expressed as folds vs. control group.

2.7. Immunoprecipitation (IP)

After treatment, 800 μg of cell lysates were pre-cleared with 20 μl of protein A/G PLUS-agarose (Santa Cruz Biotech) for 1 h. The supernatant was then rotated overnight with 2 μg of anti-MST1 (Santa Cruz Biotech). Next, lysates were centrifuged for 5 min at 4 °C in a micro-centrifuge to remove nonspecific aggregates. Protein A/G PLUS-agarose (35 μl) was then added to the supernatants for 4 h at 4 °C. Pellets were washed six times with PBS, resuspended in lysis buffer, and then assayed by immunoblotting.

2.8. Expression constructs

As previously reported [19], FLAG-tagged MST1 was cloned into a pCMV5 expression vector, and transfection was performed by Lipofectamine 2000 protocol according to instructions provided by supplier. The MST1 shRNA targeting sequence (5′-GGGCACTG TCCGAGTAGCAGC-3′ [19]) was commercially synthesized by Nanjing Genetech company (Nanjing, China), and was cloned into pSuper puro RNAi system (Addgene). Transfection was performed through Lipofectamine 2000, and stable cells was selected by puromycin. Control cells were transfected with scramble shRNA (Ctrl shRNA, addgene).

2.9. MST1 siRNA knockdown

MST1 expression was silenced using a pool of two small interfering RNAs (siRNAs) directed against the coding region of MST1

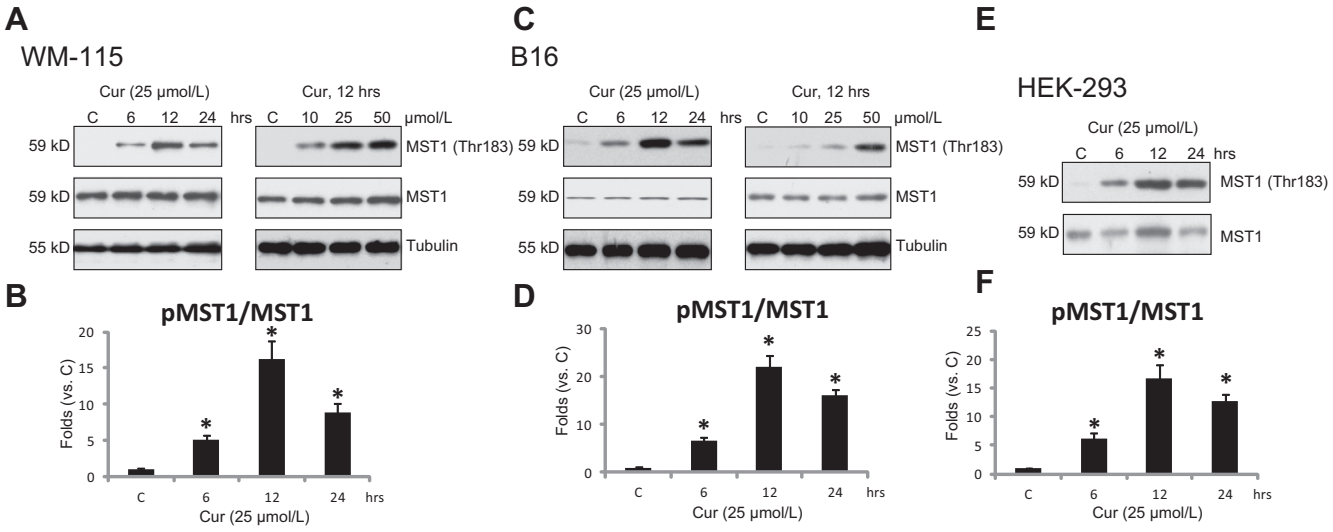

Fig. 1. Curcumin induces MST1 activation in melanoma cells. Representative immunoblots showing the expressions of phospho-MST1 (Thr 183), regular MST1 and tubulin in WM-115 (A), B16 (C) and HEK-293 (E) cells stimulated with curcumin (Cur) as indicated. Phospho-MST1 was quantified, and mean ± S.E. of three independent experiments were shown (B, D and E). *$p < 0.05$ vs. control group ("C").

(oligonucleotide 1:AAUAUUUGACUACAUGAGGGCUGUC, oligonucleotide 2, AAUGAUAUCAGAUACAGAACCAGCC, both siRNAs were not overlapping with previous shRNA sequence) [20]. siRNAs were synthesized by Nanjing Genetech company (Nanjing, China). An non-coding scramble siRNA was obtained from Santa Cruz Biotechnology (Santa Cruz, CA). Cultured melanoma cells were seeded in a 6-well plate with 60% confluence in basal medium. For transfection, 3.0 μl PLUS™ Reagent (Invitrogen, Carlsbad, CA) was diluted in 90 μl of RNA dilution water (Santa Cruz, CA) for 5 min at room temperature. Then, 0.1 nmol of MST1 siRNAs were added to PLUS™ Reagent and left for 5 min at room temperature. To this was added 4.0 μl of Lipofectamine (Invitrogen, Carlsbad, CA) and incubation for another 30 min. Finally, the complex was added to the well containing 1.0 ml of basal medium (no antibiotics, no FBS), cells then cultured for another 24 h before adding 5% FBS for another 24 h. Control cells were transfected with the same amount of scramble siRNA (100 nmol/L). Western blot analyses were carried out using antibodies against tubulin and MST1. MST1 was consistently reduced by more than 60% in cells transfected with MST1 siRNAs.

2.10. Statistical analysis

The values in the figures were expressed as the means ± standard error (SE). Statistical analysis of the data between the control and treated groups was performed by a student t test. Values of $p < 0.05$ were considered as statistically different.

3. Results

3.1. Curcumin induces MST1 activation in melanoma cells

We fist examined whether curcumin could affect MST1 activation, the latter was reflected by immunoblotting detecting phosphorylated-MST1 (Thr 183). Results in Fig. 1 demonstrated that

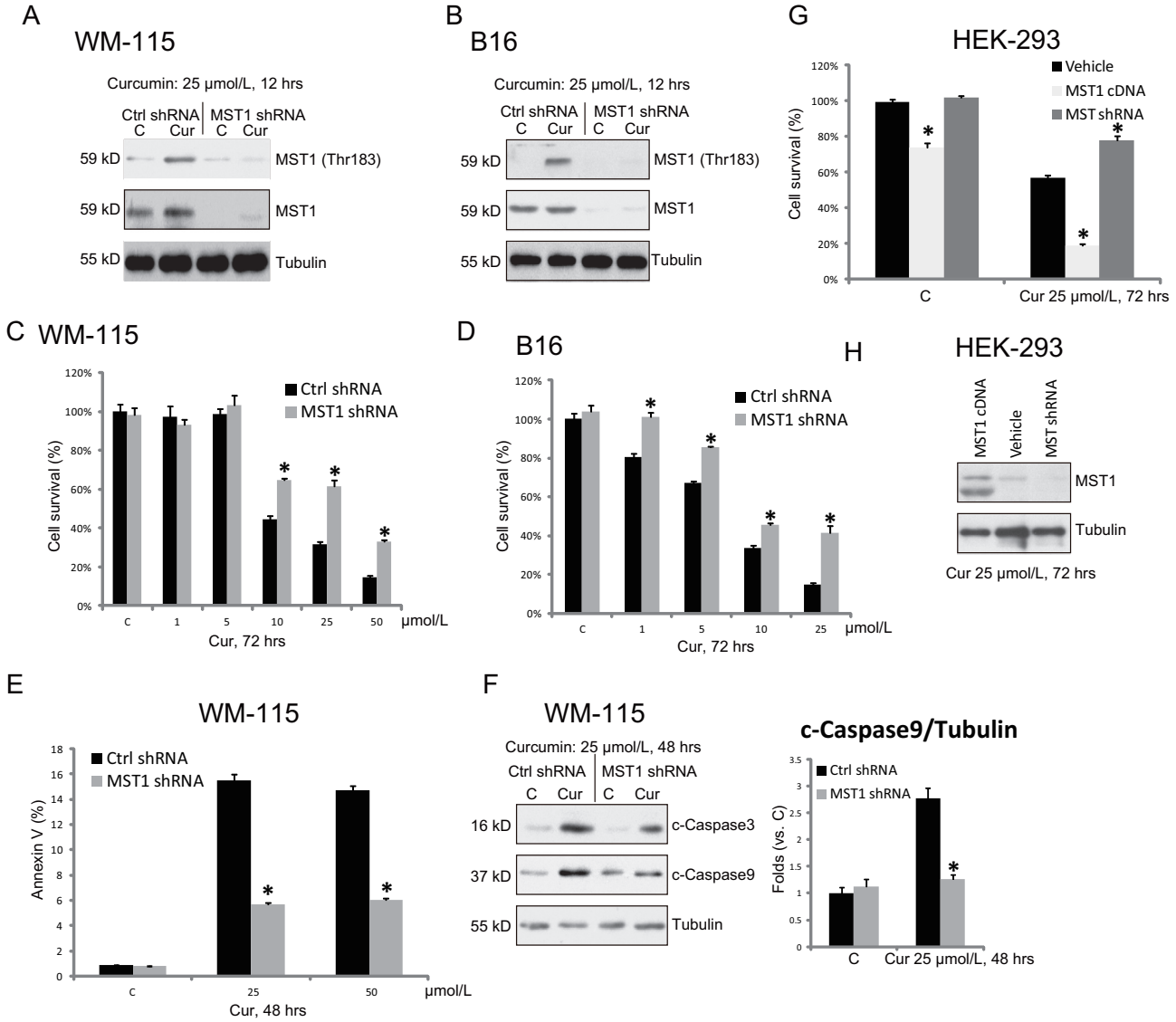

Fig. 2. MST1 mediates curcumin-induced apoptosis. Representative immunoblots showing the expressions of MST1 (phospho- and regular) and tubulin in control or MST1 shRNA expressing stable WM-115 (A) and B16 (B) cells after indicated curcumin (Cur) treatment. Above cell lines were also treated with curcumin, and cell survival was analyzed (C and D). Annexin V percentage (E) and cleaved-caspase-3/-9 expressions (F) were also examined. HEK-293 cells expressing empty vector (p-Super-puro), MST1 shRNA or MST1-FLAG were treated with curcumin, cell survival was shown (G), the expressions of MST1 and tubulin were also checked (H). Mean ± S.E. of three independent experiments were shown. *$p < 0.05$ vs. vector or control shRNA cells.

curcumin induced a significant MST1 activation in WM-115 (Fig. 1A and B) and B-16 (Fig. 1C and D) melanoma cells, as well as in HEK-293 cells (Fig. 1E and F). The effect of curcumin on MST1 activation (Thr 183 phosphorylation) was dose- and time-dependent in WM-115 (Fig. 1A) and B16 cells (Fig. 1C). Note that regular MST1 expression was not affected by curcumin in above cell lines (Fig. 1A, C and E). These results confirmed MST1 activation by curcumin in melanoma cells.

3.2. MST1 mediates curcumin-induced apoptosis

Results in Fig. 1 showed that curcumin induced MST1 activation in melanoma cells. In order to study the role of MST1 in curcumin-induced cell apoptosis, we utilized target-shRNA to knockdown MST1 in both WM-115 and B16 cells, and puromycin was applied to select stable lines. As shown in Fig. 2A and B, MST1 expression was significantly downregulated in the stable cell lines expressing MST1-shRNA (more than 90% reduction). As expected, MST1 stable knockdown abolished MST1 activation by curcumin (Fig. 2A and B). Importantly, curcumin-induced death of both WM-115 and B16 cells was largely inhibited by MST1 knockdown (Fig. 2C and D), cell death was reflected by cell survival (MTT OD) loss. Meanwhile, curcumin-induced apoptosis (Annexin V positive cells, Fig. 2E) and expression of apoptosis-associated proteins (cleaved-caspase-3/-9) (Fig. 2F) were also inhibited in MST1 stable knockdown cells. These results suggested that MST1 was required for curcumin-induced melanoma cell apoptosis. In HEK-293 cells, MST1 stable knockdown by shRNA also inhibited curcumin-induced cell survival loss, while MST1-overexpression cells were hyper-sensitive to curcumin (Fig. 2G and H).

3.3. The ROS scavenger, N-acetyl-cysteine (NAC), inhibited curcumin-induced MST1-JNK activation

It has been shown that JNK mediates MST1-dependent cell apoptosis. Previous studies including ours have shown that curcumin activates JNK through the production of ROS [7,21,22], which in turn mediates melanoma cell apoptosis [7,22]. ROS is a known activator of MST1 [13,23,24]. Immunoblots data in Fig. 3A confirmed JNK activation in curcumin-treated WM-115 cells. Meanwhile, ROS level was also increased by curcumin (Fig. 3B). Significantly, the ROS scavenger, NAC almost blocked curcumin-induced JNK and MST1 activation, suggesting ROS production might be required for MST1 and JNK activation (Fig. 3C). Notably, using the cell lines mentioned above, we found that MST1 stable knockdown dramatically inhibited curcumin-induced JNK activation in both WM-115 (Fig. 3D) and B-16 (Fig. 3E) cells, suggesting that MST1 was the upstream kinase for JNK activation in curcumin-stimulated melanoma cells.

3.4. MST1 mediates curcumin-induced Foxo3a nuclear translocation and Bim-1 expression

Previous studies have shown that MST1 directly phosphorylates Foxo3a, leading to Foxo3a disassociation with 14-3-3 and MST1, and translocation to nuclear, where it acts as a transcription factor to induce Bim-1 and other target genes expression [25]. Immunoprecipitation (IP) results in Fig. 4A showed that curcumin induced Foxo3a and MST1 disassociation in WM-115 cells, and freed Foxo3a was found to translocate to nuclear (Fig. 4B and D). Meanwhile, Bim-1 was upregulated in curcumin-treated melanoma cells

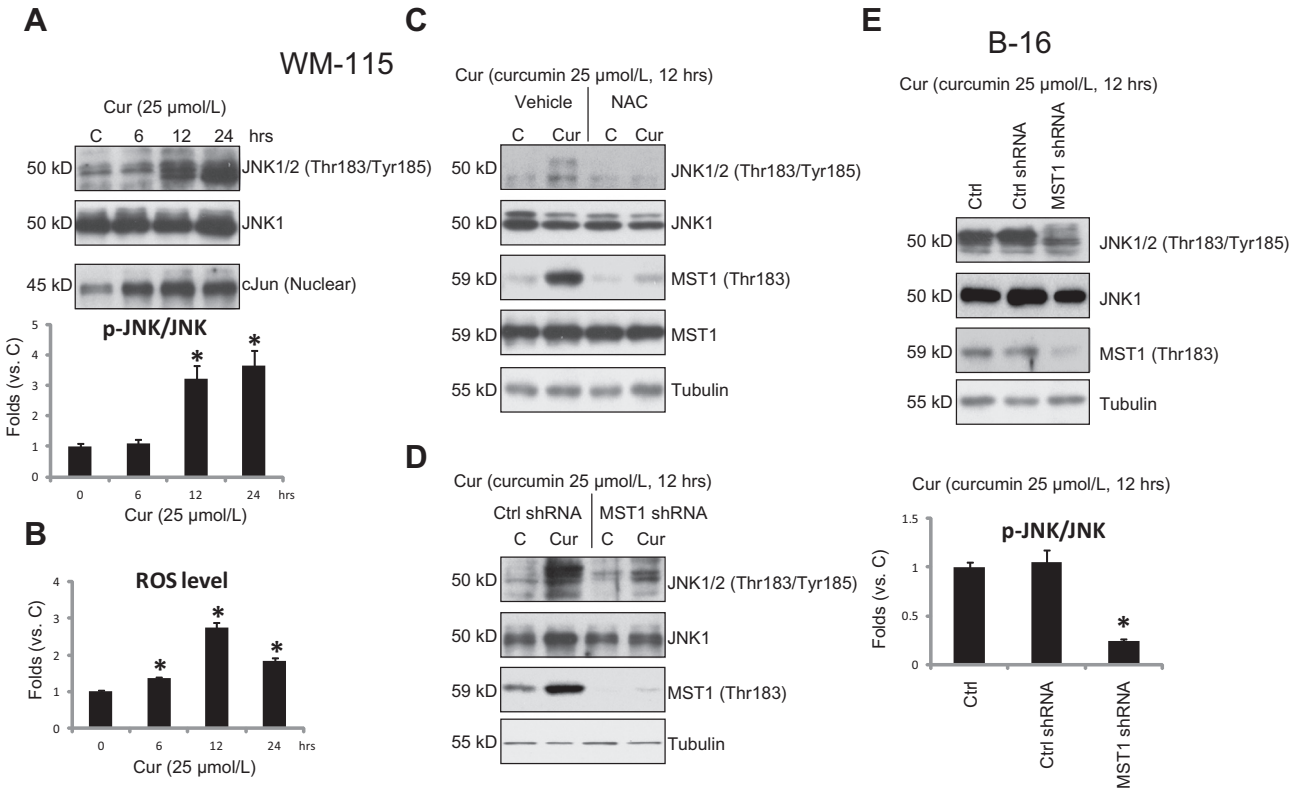

Fig. 3. The ROS scavenger, N-acetyl-cysteine (NAC) inhibited curcumin-induced MST1-JNK activation. Representative immunoblots showing the expressions of phospho-JNK1/2(Thr 183/Tyr 185) and regular JNK1 (cytosol), as well as c-Jun (nuclear) in curcumin (Cur)-treated WM-115 cells (A). ROS level (vs. control) in above cells was shown in (B). The effect of NAC (500 μmol/L, 2 h pretreatment) on curcumin-induced JNK and MST1 activation (C). Effect of MST1 stable knockdown on curcumin-induced JNK activation in WM-115 (D) and B-16 cells. (E) Mean ± S.E. of three independent experiments were shown. *$p < 0.05$ vs. control group ("C").

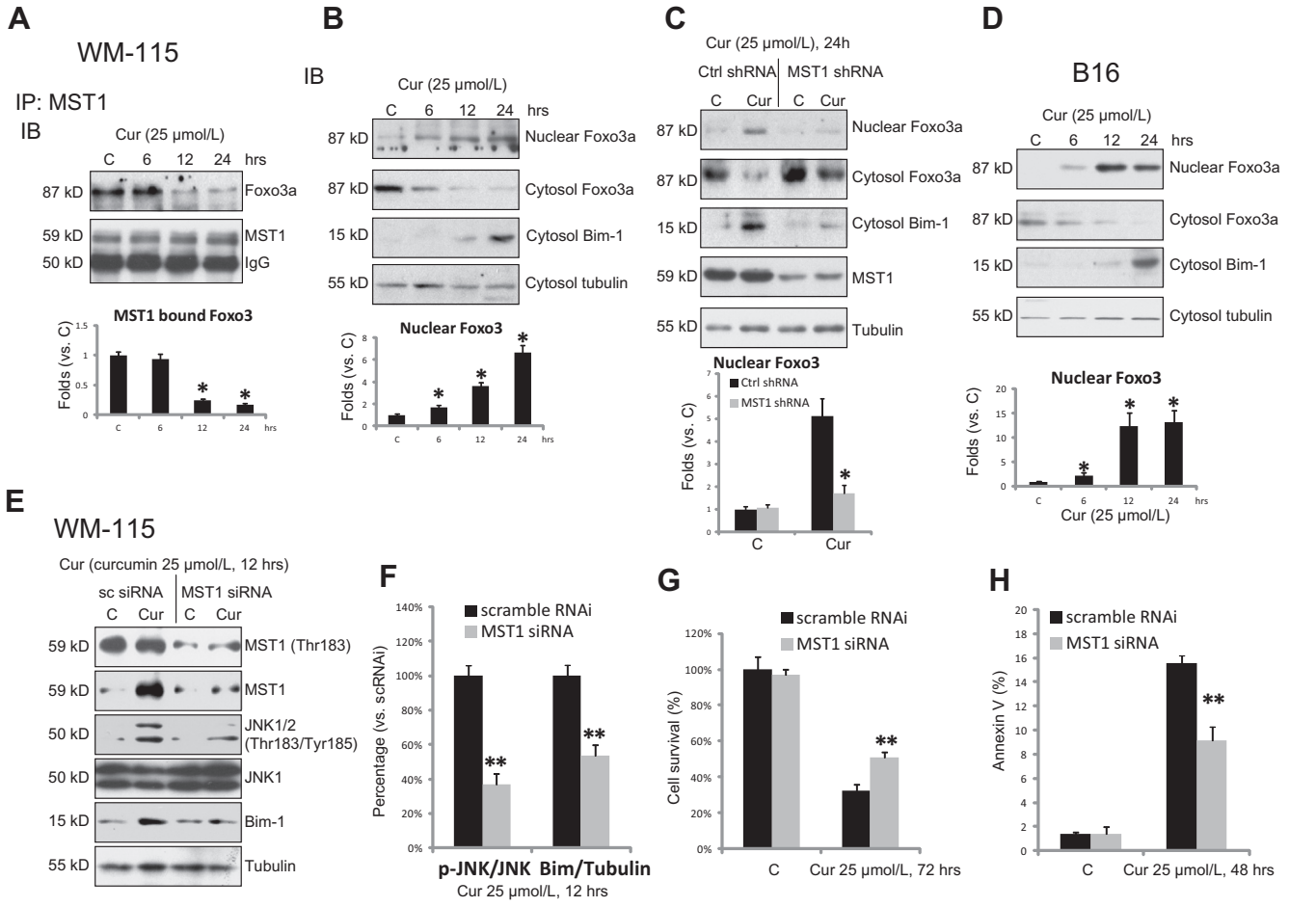

Fig. 4. MST1 mediates curcumin-induced Foxo3a nuclear translocation and Bim-1 expression. Immunoprecipitation (IP) data showing Foxo3a and MST1 disassociation after curcumin stimulation in WM-115 cells. (A) Effect of curcumin on Foxo3a nuclear translocation and Bim-1 expression in WM-115 cells. (B) Effect of MST1 shRNA knockdown on curcumin-induced Foxo3a nuclear translocation and Bim-1 expression. (C) Foxo3a and Bim expressions in both cytosol and nuclear fractions of B16 cells with curcumin stimulation. (D) WM-115 cells transfected with scramble siRNA (sc siRNA) or MST1 siRNA (100 nmol/L each) were treated with curcumin for indicated time, the expressions of phospho-MST1 (Thr 183), regular MST1, phospho-JNK1/2(Thr 183/Tyr 185), regular JNK1, Bim and tubulin were examined by western blots (E), JNK phosphorylation and Bim expression were quantified (F), cell survival (G) and apoptosis (H) were also examined. Mean ± S.E. of three independent experiments were shown. $^{*}\boldsymbol{p} < 0.05$ vs. control group ("C") (A–D). $^{**}\boldsymbol{p} < 0.05$ vs. scramble siRNA group (F–H).

(Fig. 4B and D).Importantly, MST1 stable knockdown almost blocked curcumin-induced Foxo3a nuclear translocation and Bim-1 expression (Fig. 4C and D), suggesting that MST1 mediated curcumin-induced Foxo3a nuclear translocation and Bim-1 expression, which together with JNK activation should contribute to melanoma cell apoptosis. To further confirm the role of MST1 in curcumin's effect, we transfected MST1 siRNAs (with sequence non-overlapped with previous shRNA) into cultured WM-115 cells to consistently reduce MST1 expression. As compared to cells transfected with scramble siRNA, WM-115 cells with MST1 siRNA (Fig. 4E) were resistant to curcumin-induce cell death (Fig. 4G) and apoptosis (Fig. 4H). Further, curcumin-induced JNK activation and Bim expression were also inhibited in the MST1 siRNA knockdown cells (Fig. 4E and F), similar results were also seen in B16 cells (data not shown), these results once again supported that MST1 is important for curcumin-induced JNK activation, Bim expression and cell apoptosis.

4. Discussion

Here we found that curcumin activated MST1-dependent cell apoptosis in cultured melanoma cells. MST1 stable knockdown by shRNA suppressed curcumin-induced cancer cell apoptosis, while MST1 over-expressing increased curcumin sensitivity. ROS production appeared important for curcumin-induced activation of MST1, and activated MST1 promoted melanoma cell apoptosis probably through inducing JNK activation, Foxo3a nuclear accumulation and Bim-1 expression. We concluded that MST1 is required for curcumin-induced melanoma cell apoptosis.

Studies have shown that curcumin induces the activation of caspase-3 and caspase-9 through cleavage. In addition, z-VAD-fmk, the universal caspases inhibitor, prevents caspases activation and inhibits curcumin-induced cancer cell death [26–28]. Meanwhile, curcumin was found to induce Bim expression in multiple cancer cells [28,29]. In the current study, we also observed caspase-3/-9 cleavage and Bim expression in curcumin treated melanoma cells, and MST1 silencing inhibited such effects by curcumin. Thus, MST1 activation might also be required for curcumin-induced caspases activation and Bim expression, which contributed to cancer cell apoptosis.

JNK (also known as SAPK) is implicated in apoptosis induction in many systems [30]. It is potently activated by environmental stresses and pro-inflammatory cytokines that induce apoptosis [31]. Previous studies [22,32] including ours [7] have shown that curcumin activates JNK in melanoma cells which plays an important role in mediating cell apoptosis [7]. On the other hand, inhibition of JNK suppressed cancer cell death by curcumin [7,12,21,32]. How JNK is activated by curcumin is not fully addressed. Here we

provided evidence to suggest that ROS-activated MST1 activation might be the upstream kinase for curcumin-induced JNK activation, based on the fact that ROS scavenger NAC and MST1 silencing almost blocked curcumin-induced JNK activation in melanoma cells. MST1 is an known upstream kinase of JNK [33], and MST1 mediated cell apoptosis relies on, at least in part, by JNK activation [33]. Meanwhile, a dominant-negative mutant of JNK was found to inhibit MST1-induced caspase activation and cell apoptosis [33]. Thus, we indentified a potential upstream kinase for JNK activation by curcumin.

The Foxo3 transcription factor induces apoptotic response in mammalian cells upon exposure to stress conditions [34,35]. Recent studies have shown that curcumin activated Foxo transcription to promote apoptosis in lymphoblastic leukemia T cells [27], and the underlying mechanism associated was not clear. It has been recently shown that Foxo3 is the evolutionarily conserved target of the MST1 [25]. Under oxidative stress, MST1 is activated which in turn directly phosphorylates Foxo3 at serine 207 [25]. The MST1-induced phosphorylation of Foxo3 disrupts Foxo3's interaction with 14-3-3, promotes Foxo3 translocation to the nucleus, and thereby induces its target gene (i.e. Bim-1) expression to mediate cell apoptosis. In the current study, Foxo3a was also found to translocate to nuclear after curcumin treatment, and its target gene Bim-1 was upregulated. MST1 stable knockdown blocked Foxo3a nuclear translocation and Bim-1 expression by curcumin. Thus we proposed the following model: in melanoma cells, curcumin induces ROS production to activate MST1, which directly phosphorylates Foxo3 [25], causing it nuclear translocation, where it promotes Bim-1 upregulation and cell apoptosis. More directly evidences are needed to further support hypothesis.

Acknowledgments

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