Metabolic Brain Disease (2019) 34:61–69
https://doi.org/10.1007/s11011-018-0319-y

ORIGINAL ARTICLE

Role of PUMA in the methamphetamine-induced migration of microglia

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Received: 4 April 2018 / Accepted: 17 September 2018 / Published online: 26 September 2018

Abstract

In this study, we demonstrated that PUMA was involved in the microglial migration induced by methamphetamine. PUMA expression was examined by western blotting and immunofluorescence staining. BV2 and HAPI cells were pretreated with a sigma-1R antagonist and extracellular signal-regulated kinase (ERK), mitogen-activated protein kinase (MAPK), c-Jun N-terminal protein kinase (JNK), and phosphatidylinositol-3 kinase (PI3K)/Akt inhibitors, and PUMA expression was detected by western blotting. The cell migration in BV2 and HAPI cells transfected with a lentivirus encoding red fluorescent protein (LV-RFP) was also examined using a wound-healing assay and nested matrix model and cell migration assay respectively. The molecular mechanisms of PUMA in microglial migration were validated using a siRNA approach. The exposure of BV2 and HAPI cells to methamphetamine increased the expression of PUMA, reactive oxygen species (ROS), the MAPK and PI3K/Akt pathways and the downstream transcription factor signal transducer and activator of transcription 3 (STAT3) pathways. PUMA knockdown in microglia transfected with PUMA siRNA attenuated the increased cell migration induced by methamphetamine, thereby implicating PUMA in the migration of BV2 and HAPI cells. This study demonstrated that methamphetamine-induced microglial migration involved PUMA up-regulation. Targeting PUMA could provide insights into the development of a potential therapeutic approach for the alleviation of microglia migration induced by methamphetamine.

Keywords PUMA · Methamphetamine · Microglia · Migration

Introduction

Methamphetamine has a highly addictive effect on the central nervous system (CNS) and is abused worldwide (Krasnova et al. 2016; Saika et al. 2015). Methamphetamine abuse, including both acute and chronic use, is a serious public health problem because of its adverse effects, including hyperthermia, disruption of the blood-brain barrier, edema and cognitive impairment (Harro 2015; Sharma and Kiyatkin 2009).

Microglia are resident immune cells that are involved in innate inflammatory responses in the CNS (Yao et al. 2014). Microglia have the capacity to rapidly return an injured tissue back to normal homeostasis, so they are critical for maintaining a healthy tissue environment. This response requires migration of microglia to the damaged area and phagocytosis of aberrant material. In response to pathological stimuli, microglia undergo phenotypic changes, trigger inflammatory responses and migrate towards the toxic stimuli. While crucial for host defense, microglia can also lead to neuropathological changes if the inflammatory response remains unchecked (Rostasy 2005). Understanding the regulation of microglial migration is important to comprehend the inflammatory processes extant in the neuropathology. In vivo live imaging studies have shown that microglia actively migrate toward pathological stressors (Peri and Nusslein-Volhard 2008; Venneti et al. 2009), and at the same time, microglia also have other critical functions, including elaboration of immunomodulatory substances and cytotoxic factors, phagocytosis, and

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coordination of the adaptive immune response (Lull and Block 2010). Hickman and El Khoury have confirmed that the ability of microglia to migrate into and through brain parenchyma in response to various stressors is critical to their physiological and pathophysiological actions and is dependent on recognition of diverse external stimuli by cell surface receptors that mediate microglial migration and other functions via converging signaling pathways (Hickman and El Khoury 2010). Increased numbers of microglia and a proinflammatory environment are characteristic features of many neurological disorders, such as Alzheimer's disease, Parkinson's disease, stroke, and traumatic brain injury. Microglia can serve neurotoxic as well as neuroprotective functions, and both depend on their ability to migrate toward an injury focus. It is crucial to understand the mechanisms of microglial migration for the development of strategies to elucidate their role in neuropathological states and identification of therapeutic targets in neuritic and neurodegenerative diseases.

PUMA (p53-up-regulated modulator of apoptosis) is a pro-apoptotic protein of the BH3-only subgroup of the Bcl-2 family, and it is a critical mediator of p53-dependent and p53-independent apoptosis that produces a strong apoptotic effect (Hikisz and Kilianska 2012; Vavrova and Rezacova 2014). PUMA expression is strongly correlated with apoptosis, and the ectopic expression of PUMA is sufficient to elicit apoptosis in neuronal cell cultures (Cregan et al. 2004). Furthermore, PUMA-deficient neurons are substantially more resistant to cell death induced by the over-expression of p53. Thus, PUMA is a potent inducer of p53-mediated neuronal apoptosis. Our previous study indicated that knockdown of PUMA abolished the fibroblast proliferation and migration increase during silicosis (Wang et al. 2015). We also provided direct evidence that methamphetamine induced pericyte migration, thereby contributing to BBB damage in drug abusers via a previously unidentified role of PUMA. However, the role of PUMA in the inflammatory response and migration of microglia in methamphetamine abusers is unknown.

Thus, in the current study, we provide direct evidence that methamphetamine induces microglial migration, thereby contributing to the neuroinflammation that leads to increased PUMA expression in drug abusers. This study suggests that targeting PUMA could provide a potential therapeutic approach to alleviate microglial migration in neuroinflammation induced by methamphetamine.

Materials and methods

Reagents

Methamphetamine was purchased from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). The specific extracellular signal-regulated kinase (ERK) inhibitor U0126, the c-Jun N-terminal protein kinase (JNK) inhibitor SP600125, the p38 mitogen-activated protein kinase (MAPK) inhibitor SB203580 and the phosphatidylinositol-3′ kinase (PI3K) inhibitor LY294002 were purchased from Calbiochem (San Diego, CA, USA). The concentrations of these inhibitors were based on a concentration-curve study and our previous reports (Yao et al. 2010). The sigma-1 receptor (sigma-1R) antagonist BD1047 and the signal transducer and activator of transcription 3 (STAT3) inhibitor stattic were obtained from Sigma-Aldrich (St. Louis, MO, USA).

Cell culture

BV2 and HAPI cells were purchased from the China Center for Type Culture Collection (Wuhan, China), cultured in high-glucose Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% FBS and 1% penicillin/streptomycin and incubated in a CO_2 incubator (Thermo Con Electron Corporation, Waltham, MA, USA) at 37 °C with a humidified atmosphere of 5% CO_2 and 95% air. BV2 and HAPI cells were used between P6 and P16.

Western blotting

BV2 and HAPI cells were lysed using either the Mammalian Cell Lysis Kit (Sigma-Aldrich, St. Louis, MO, USA) or the NE-PER Nuclear and Cytoplasmic Extraction Kit (Pierce, Rockford, IL, USA). Equal amounts of sample proteins were loaded on a 12% polyacrylamide gel, followed by transfer to polyvinylidene difluoride (PVDF) membranes, which were blocked with buffer containing 5% non-fat dry milk in Tris-buffered saline with Tween-20. The membranes were then incubated with primary antibodies against PUMA (1:1000; Cell Signaling, Danvers, MA, USA), STAT3 (1:1000; Proteintech, Chicago, IL, USA), followed by secondary antibodies (horseradish peroxidase-conjugated to goat anti-mouse/rabbit IgG at 1:2000). β-actin (1:1000; Sigma-Aldrich, St. Louis, MO, USA) was employed as loading controls. Immunoblots were visualized using Millipore ECL Western Blotting Detection System (Millipore, Billerica, MA, USA). Quantification was performed by densitometry using ImageJ software (NIH).

Immunofluorescence staining

BV2 cells were cultured on cover-slips and then treated with methamphetamine for 12 h. The cells were fixed with 4% formaldehyde in phosphate-buffered saline (PBS), permeabilized with 0.3% Triton X-100 in PBS,

blocked with 10% normal goat serum (NGS) in 0.3% Triton X-100, and then incubated with rabbit anti-PUMA (1:250; Cell Signaling, Danvers, MA, USA) at 4 °C overnight. The cells were incubated with an Alexa Fluor 488-conjugated anti-rabbit IgG secondary antibody (1:250; Invitrogen/Life Technologies, Grand Island, NY, USA) and mounted onto slides with mounting medium (Prolong Gold Anti-fade Reagent; Invitrogen/Life Technologies, Grand Island, NY, USA). PUMA expression was examined using an Olympus FV 1000 microscope.

Cell migration assay

The cell migration abilities were detected using a wound-healing assay. The cells were seeded in a 24-well plate and incubated to 70–80% confluence. A cell-free straight line was then created in the center of the well by scratching with a sterile 10-μl pipette tip. Similarly, a second straight line was scratched perpendicularly to the first line to create a cross-shaped cellular gap in each well.

A nested collagen matrix model was used. First, a standard fibroblast-populated collagen matrix (FPCM) was incubated in an attached state for 72 h in DMEM containing 10% FBS. Then, the FPCM was removed from the well and placed in a 70-μl aliquot of fresh acellular collagen matrix solution (a NeoMatrix solution) that was centered within a 12-mm diameter score on the bottom of a new culture well. Last, a 130-μl aliquot of NeoMatrix solution was used to cover the newly transferred FPCM. The NeoMatrix was allowed to polymerize for 1 h at 37 °C in 5% CO_2, and 1 ml of DMEM containing 10% FBS was then added to the well.

Cells migration was quantified via fluorescence microscopy at 24 h after methamphetamine treatment. Cell migration from the nested FPCM were quantified by counting the number of cells that had clearly migrated from the nested matrix to the cell-free matrix. Digital images of the cell gap were captured at different time points, and the gap width was quantitatively evaluated using ImageJ software.

Statistical analysis

The statistical analysis was performed using SigmaPlot software (SigmaPlot 11.0, Systat, Inc.). Data are presented as the mean ± SD, and the experiments were repeated at least three times individually. The significance of the differences between the control and the samples treated with various drugs was tested using one-way ANOVA. A p value <0.05 was considered statistically significant.

Results

Sigma-1R mediated the methamphetamine-induced PUMA up-regulation in microglia

Little is known about the role of sigma-1R in methamphetamine-mediated microglial polarization. According to our previous study (Zhang et al. 2015), a 150 μM concentration of methamphetamine was the optimal dose to induce microglial activation. To assess the time course of the action of methamphetamine, we exposed the BV2 and HAPI cells to 150 μM for varying time intervals. Methamphetamine treatment of the microglia resulted in increased PUMA expression. However, the expression of sigma-1R in BV2 cells has also been implicated, and sigma-1R interacts with methamphetamine at physiologically relevant concentrations (Gekker et al. 2006; Seminerio et al. 2012). To determine whether the sigma-1R is involved in the methamphetamine-induced PUMA up-regulation, BV2 and HAPI cells were pretreated with the sigma-1R antagonist BD1047, followed by methamphetamine treatment. As shown in Fig. 1a–d, pretreatment of BV2 and HAPI cells with BD1047 (10 μM) significantly inhibited the increase in PUMA expression. This finding was further confirmed by immunostaining. As shown in Fig. 1e, the methamphetamine treatment increased the expression of PUMA, which was inhibited by the sigma-1R antagonist BD1047.

ROS, MAPKs and PI3K/Akt pathways were involved in the methamphetamine-induced PUMA up-regulation in microglia

Oxidative stress is known to be involved in methamphetamine-induced dopaminergic neurotoxicity (Riddle et al. 2006). Since the sigma-1R-mediated generation of ROS and the activation of signaling pathways are two critical processes involved in microglial polarization, we used a pharmacological approach to determine whether there was a link between ROS formation and signal transduction pathways. BV2 and HAPI cells were pretreated with the NADPH oxidase inhibitor apocynin, followed by treatment with methamphetamine. As shown in Fig. 2a–d, pretreatment of BV2 and HAPI cells with the ROS inhibitor apocynin (10 μM) significantly inhibited the up-regulation of PUMA. Several studies have implicated the MAPK and PI3K/Akt pathways in methamphetamine-mediated signaling (Gonzalez et al. 2014; Ma et al. 2014; Wang et al. 2008). Because methamphetamine up-regulated the expression of PUMA and activated the MAPK and PI3K/Akt pathways, we then investigated the link between PUMA expression and the MAPK and PI3K/Akt pathways. We pretreated BV2 and HAPI cells with an ERK inhibitor (U0126, 10 μM), a MAPK inhibitor (SB203580, 10 μM), a JNK inhibitor

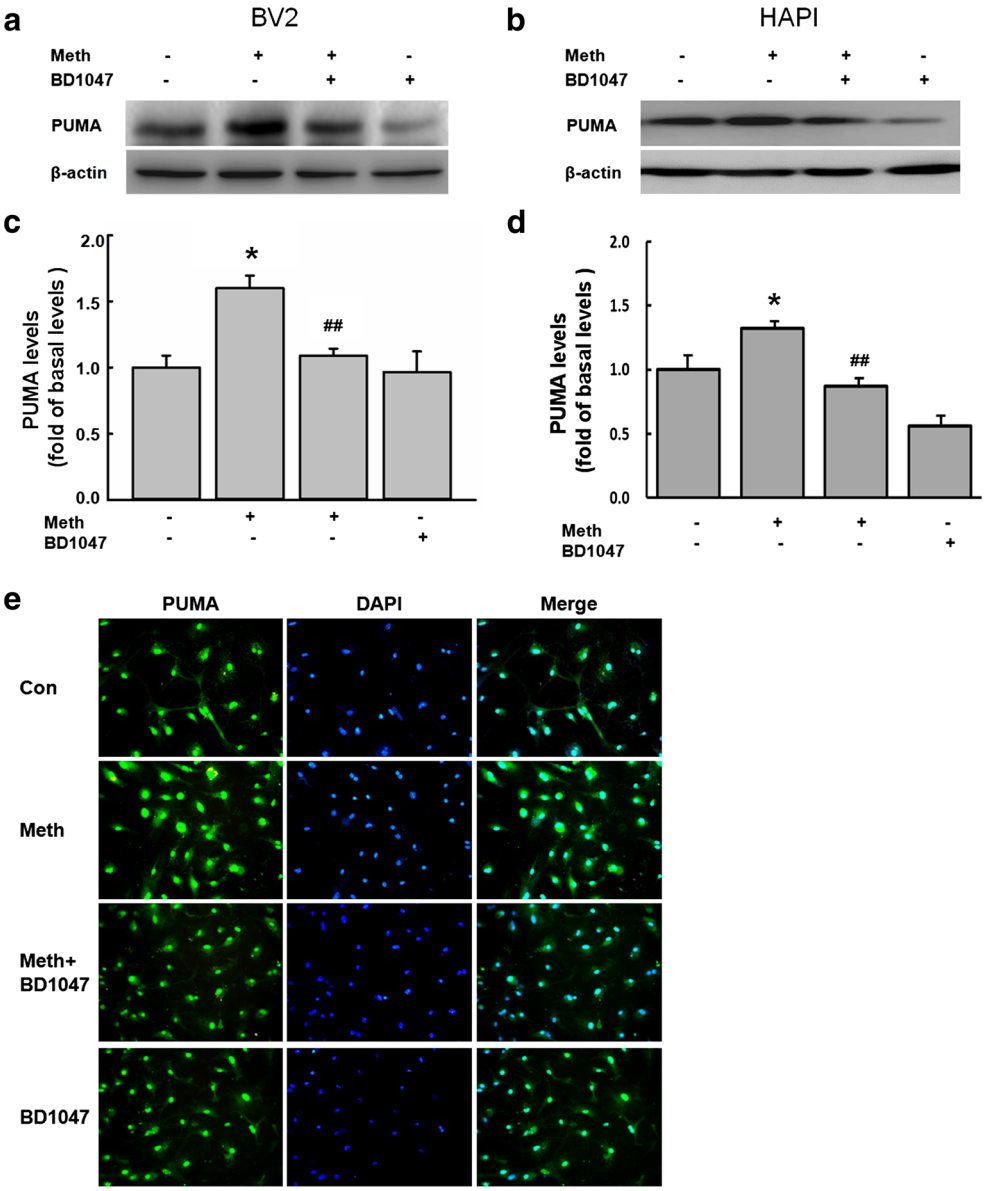

Fig. 1 Sigma-1R mediated the methamphetamine-induced up-regulation of PUMA in microglia. **a**, **b** Representative western blot showing the effects of methamphetamine (150 μM) on the increase in PUMA expression, which was attenuated by a sigma-1R antagonist (BD1047, 10 μM) in BV2 and HAPI cells. **c**, **d** Densitometric analyses suggested that methamphetamine increased PUMA expression, which was attenuated by BD1047 pretreatment. **e** Representative image of PUMA immunostaining in BV2 cells after treatment with methamphetamine and with BD1047 pretreatment. * $p < 0.05$ vs the control group; $^{\#\#}p < 0.01$ vs the methamphetamine-treated group using one-way ANOVA. Meth, methamphetamine

(SP600125, 10 μM) and a PI3K/Akt inhibitor (LY294002,10 μM) for 1 h, followed by treatment with methamphetamine for an additional 3 h. As shown in Fig. 3a–d, the methamphetamine-mediated increased expression of PUMA was significantly inhibited by pretreatment with these inhibitors, except for the ERK inhibitor.

Involvement of STAT3 in the methamphetamine-induced increase in PUMA expression

The upstream signaling pathways, e.g., the MAPK and PI3K/Akt pathways, were involved in the methamphetamine-mediated increase in PUMA expression. Then, we sought to determine whether PUMA up-regulation involved the downstream molecule STAT3. Our previous study demonstrated that methamphetamine increased the expression of STAT3 with a concomitant increase in the translocation of STAT3 into the nucleus, and the maximal response occurred within 30 min. As shown in Fig. 4a and b, the activation of STAT3 significantly increased the expression of PUMA after BV2 cells were pretreated with methamphetamine. Similar to our studies described above, the pretreatment of BV2 cells with the STAT3 inhibitor stattic inhibited the methamphetamine-mediated increase of PUMA expression (Fig. 4c and d).

PUMA mediated the methamphetamine-induced migration of microglia

In addition to the activation of microglia, reactive microglia also migrate to injured sites and orchestrate an inflammatory

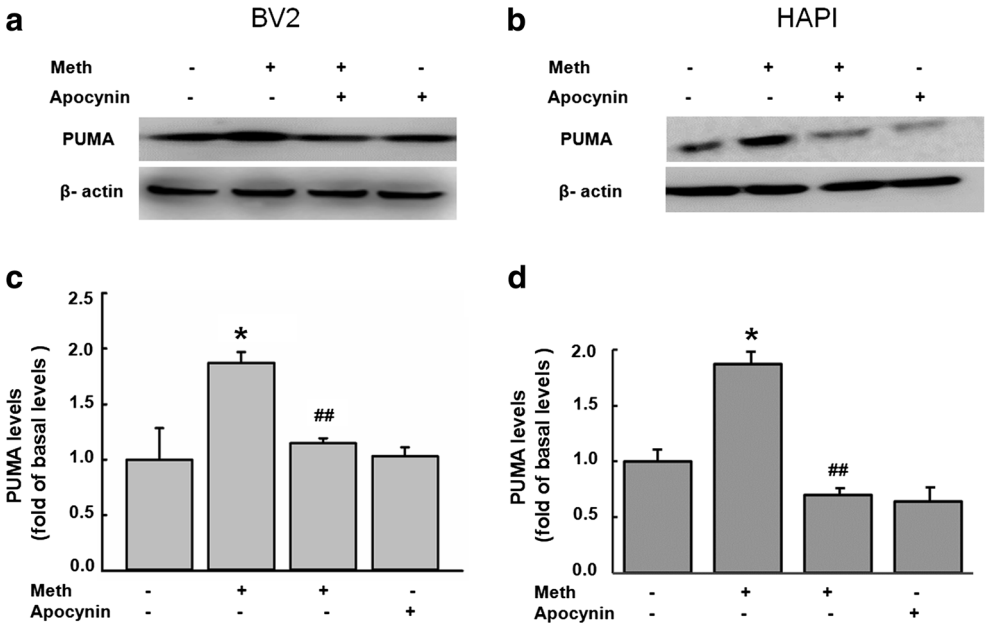

Fig. 2 ROS was involved in the methamphetamine-induced up-regulation of PUMA in microglia **a**, **b** Representative western blot showing the effects of methamphetamine on the increase in PUMA expression, which was attenuated by a ROS inhibitor (apocynin, 10 μM) in BV2 and HAPI cells. **c**, **d** Densitometric analyses suggested that methamphetamine increased PUMA expression, which was attenuated by the apocynin pretreatment. * $p < 0.05$, ** $p < 0.01$ vs the control group; ## $p < 0.01$ vs the methamphetamine-treated group using one-way ANOVA. Meth, methamphetamine

response. Therefore, we determined the role of PUMA in the migration of microglia mediated by methamphetamine. The wound-healing assay showed that methamphetamine time-dependently increased microglial migration in BV2 cells (Fig. 5a). The transfection of the cells with PUMA siRNA inhibited methamphetamine-induced migration of BV2 cells (Fig. 5b). The nested matrix model and cell migration assay showed that methamphetamine time-dependently increased microglial migration in HAPI cells (Fig. 5c), further supporting the role of PUMA in this process.

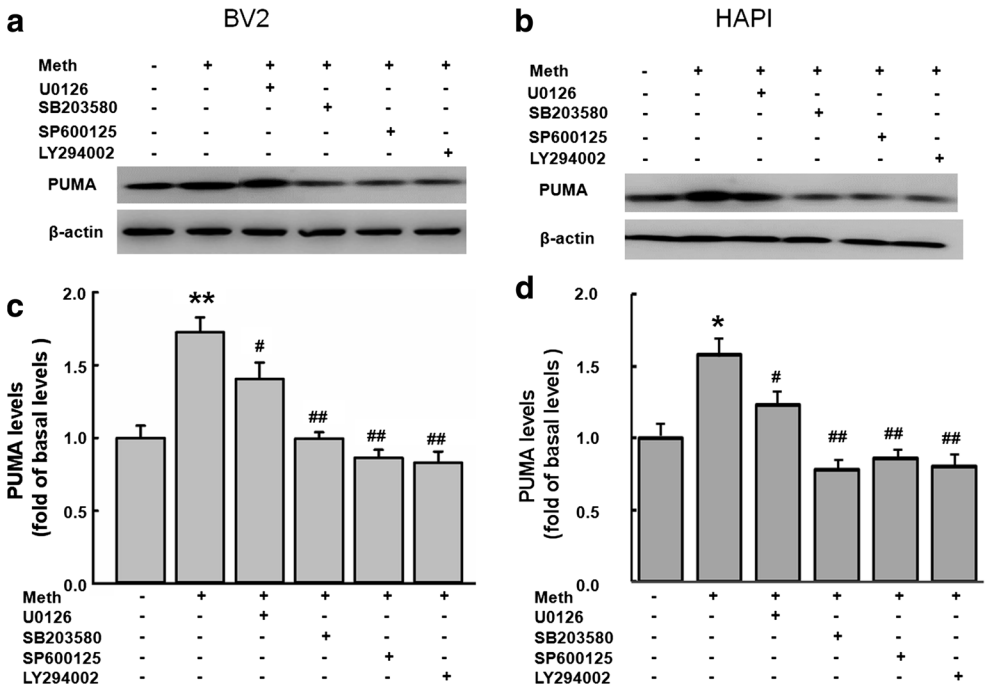

Fig. 3 The MAPK and PI3K/Akt pathways were involved in the methamphetamine-induced up-regulation of PUMA in microglia. **a**, **b** Representative western blot showing the effects of methamphetamine on the increase in PUMA expression, which was attenuated by the MAPK inhibitor (SB203580, 10 μM), the JNK inhibitor (SP600125, 10 μM) and the PI3K/Akt inhibitor (LY294002, 10 μM) but not the ERK inhibitor (U0126, 10 μM) in BV2 and HAPI cells. **c**, **d** Densitometric analyses suggested that methamphetamine increased PUMA expression, which was attenuated by the SB203580, SP600125 and LY294002 pretreatments but not the U0126 pretreatment. * $p < 0.05$, ** $p < 0.01$ vs the control group; ## $p < 0.01$ vs the methamphetamine-treated group using one-way ANOVA. Meth, methamphetamine

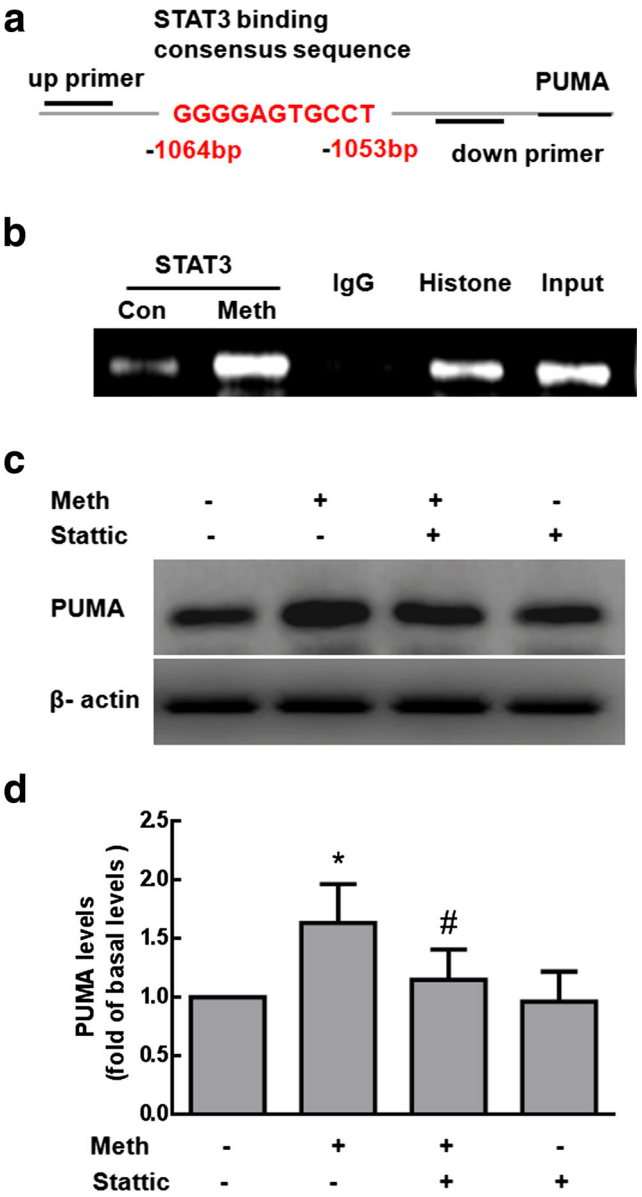

Fig. 4 Involvement of STAT3 in the methamphetamine-induced increase of PUMA expression. **a**, **b** Representative immunoprecipitation assay showing the effects of methamphetamine on the increase in PUMA expression following the activation of STAT3 in BV2 cells. **c**, **d** Densitometric analyses suggested that methamphetamine increased PUMA expression, which was attenuated by the STAT3 inhibitor (stattic, 10 μM) pretreatment. ** $p < 0.01$ vs the control group; ## $p < 0.01$ vs the methamphetamine-treated group using one-way ANOVA. Meth, methamphetamine

Discussion

Previous studies have demonstrated that PUMA was involved in the microglial activation induced by methamphetamine (McConnell et al. 2015; Robson et al. 2013; Shin et al. 2014); however, whether PUMA mediates microglial migration and the molecular mechanisms underlying this process have not been elucidated. The present study demonstrated that PUMA was involved in microglial migration, as well as its related mechanisms.

Regarding methamphetamine-induced neuroinflammation, mounting evidence has demonstrated that administration of methamphetamine could induce a substantial inflammatory response (McConnell et al. 2015). Up-regulated inflammatory mediators and proliferation of microglia were highly correlated with subsequent methamphetamine-induced neurotoxicity. The methamphetamine-induced microglial activation preceded the neuronal damage and response to methamphetamine application in a dose-dependent manner, suggesting a specific causal relationship with methamphetamine-induced neurotoxicity (Thomas et al. 2004). Migration is a critical incident of microglial activation in response to pathological stimuli. The capacity of microglia to rapidly return an injured tissue back to normal homeostasis is crucial to maintain a healthy tissue environment. In this study, we demonstrated that methamphetamine exposure increased PUMA expression in the microglia via the methamphetamine cognate receptor, sigma-1R, which induced ROS generation and the activation of the MAPK and PI3K/Akt pathways, followed by the subsequent translocation of STAT3, ultimately leading to PUMA up-regulation and migration of microglia. To the best of our knowledge, these results demonstrated for the first time the critical role of PUMA in methamphetamine-mediated migration of microglia.

Consistent with previous studies, the inhibition of sigma-1R by the antagonist BD1047 significantly blocked the methamphetamine-induced microglial polarization, and our in vivo study further confirmed that blockade of sigma-1R alleviated the microglial activation induced by methamphetamine using a genetic approach with a sigma-1R KO animal model (Yao et al. 2014). In this study, we determined that methamphetamine treatment increased the expression of PUMA, which was inhibited by the sigma-1R antagonist BD1047. These results clearly demonstrated that sigma-1R is involved in the methamphetamine-induced PUMA up-regulation in microglia.

Increased levels of ROS are linked with microglial activation and the secretion of inflammatory factors (Li et al. 2015; Liao et al. 2016; Shi et al. 2016). Our previous study showed that sigma-1R/lipid rafts played a critical role in the NADPH-mediated ROS generation in cocaine-exposed microglia (Yao et al. 2010), and interestingly, the inhibition of BV2 and HAPI cells by BD1047 significantly attenuated ROS production, suggesting that the activation of the sigma-1R lies upstream of the methamphetamine-mediated ROS generation. We also determined that pretreatment of BV2 and HAPI cells with the ROS inhibitor apocynin significantly inhibited the up-regulation of PUMA. Our study revealed that methamphetamine mediated the phosphorylation of the ERK, JNK, p38 MAPK and PI3K/Akt pathways in microglial migration, and then, we investigated the link between the expression of

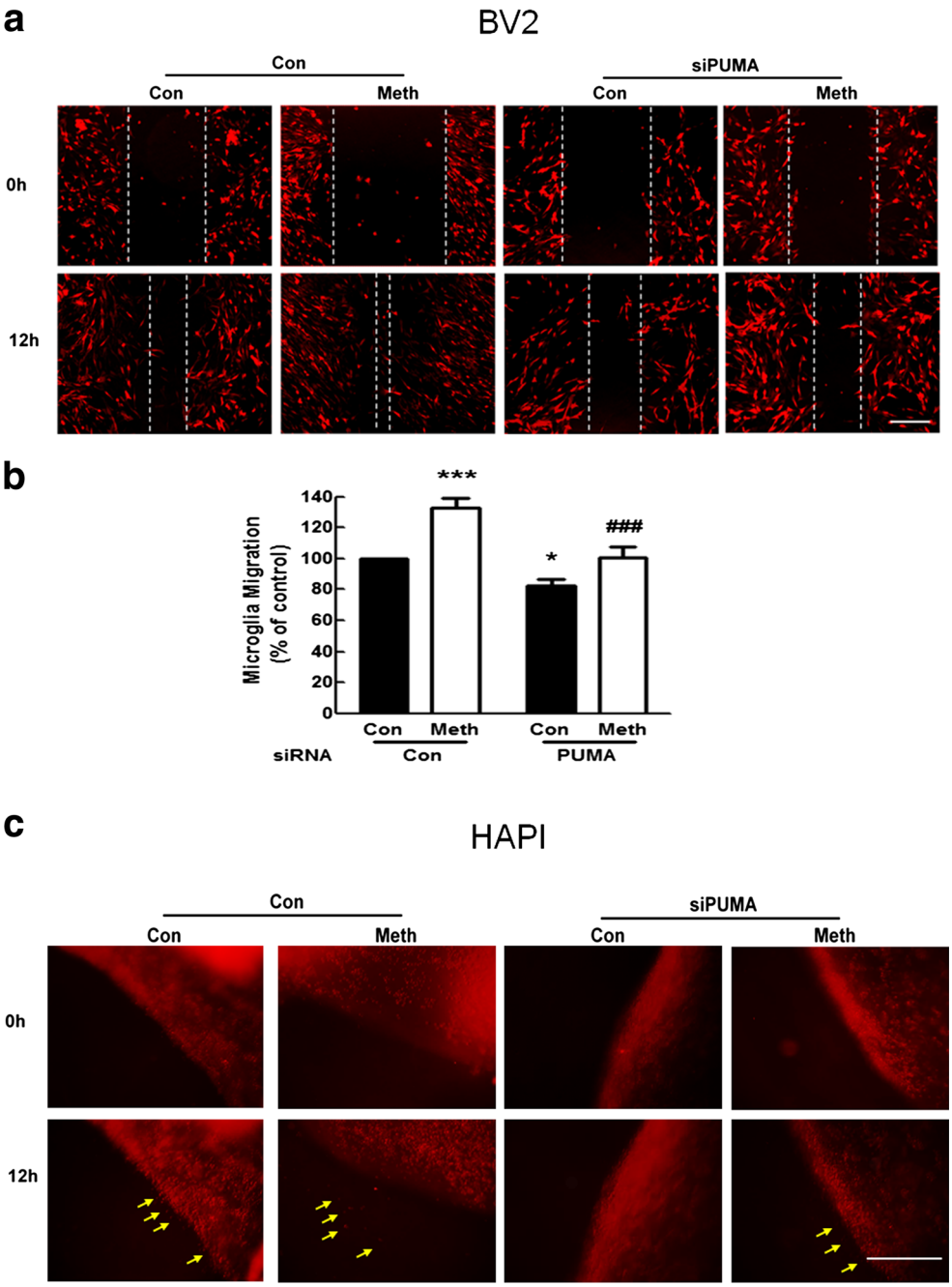

Fig. 5 PUMA mediated the methamphetamine-induced migration of microglia. **a** A wound-healing assay showed that methamphetamine time-dependently increased cell migration in BV2 cells, but transfection of BV2 cells with siPUMA inhibited the methamphetamine-mediated induction of BV2 cell migration. Scale bars all indicate 500 μm. The gap widths from three separate experiments were quantitatively evaluated using ImageJ software. **b** Densitometric analyses suggested that methamphetamine induced BV2 cell migration, which was attenuated by the siPUMA transfection. **c** A nested matrix model and cell migration assay showed that methamphetamine time-dependently increased cell migration quantity and distance in HAPI cells, but transfection of HAPI cells with siPUMA inhibited the methamphetamine-mediated induction of HAPI cell migration. Scale bars all indicate 500 μm. The gap widths from three separate experiments were quantitatively evaluated using ImageJ software. * $p < 0.05$, *** $p < 0.001$ vs the control group; ### $p < 0.001$ vs the methamphetamine-treated group using one-way ANOVA. Meth, methamphetamine

PUMA and these pathways. The methamphetamine-mediated increase in PUMA expression was significantly reduced by pretreatment with these inhibitors, except for the ERK inhibitor. Thus, the sigma-1R-mediated ROS generation lies upstream of the phosphorylation of the JNK, p38 MAPK and PI3K/Akt cascades following methamphetamine induction.

STAT3 is a member of the STAT protein family. In response to cytokines and growth factors, STAT3 is phosphorylated by receptor-associated Janus kinases (JAK), forms homo- or heterodimers, and translocates to the cell nucleus, where it acts as transcription activators. STAT3 is mainly expressed in glial cells (LeComte et al. 2015; Liu et al. 2015) and is involved in inflammatory responses (Deguchi 2015; Muhl 2016). The methamphetamine exposure induced a time-dependent STAT3 protein increase and the translocation of STAT3 into the nucleus. Using a pharmacological approach, we found that signaling pathways involved in the methamphetamine-mediated translocation of STAT3 contained the upstream JNK, p38 MAPK and PI3K/Akt pathways. In this study, we determined that the activation of STAT3 significantly increased the expression of PUMA after BV2 cells were pretreated with methamphetamine.

Pretreatment of BV2 cells with the STAT3 inhibitor stattic inhibited the methamphetamine-mediated increase of PUMA expression.

PUMA is a member of the BH3-only protein family and is an essential apoptosis inducer (Chipuk et al. 2005; Vousden 2005). Moreover, while PUMA is highly expressed in microglia, it has not been shown to induce apoptosis in these cells, and little is known regarding the function of PUMA in microglia. Microglial migration and activation are critical features of the neuroinflammatory process (Xiong et al. 2016; Yuan et al. 2016), neuroinflammation is a key feature of most neurodegenerative diseases, and microglia have critical roles in the process of neuroinflammation (Wake et al. 2013). Our studies provide evidence that methamphetamine time-dependently induced microglial migration in BV2 and HAPI cells. The transfection of the cells with PUMA siRNA resulted in the inhibition of the methamphetamine-induced migration. Thus, PUMA plays a key role in methamphetamine-mediated microglial migration in our studies. To our knowledge, this is the first report to demonstrate that PUMA mediated microglial migration induced by methamphetamine, indicating that PUMA is a promising therapeutic target for the amelioration of methamphetamine-mediated neuroinflammation orchestrated by microglia.

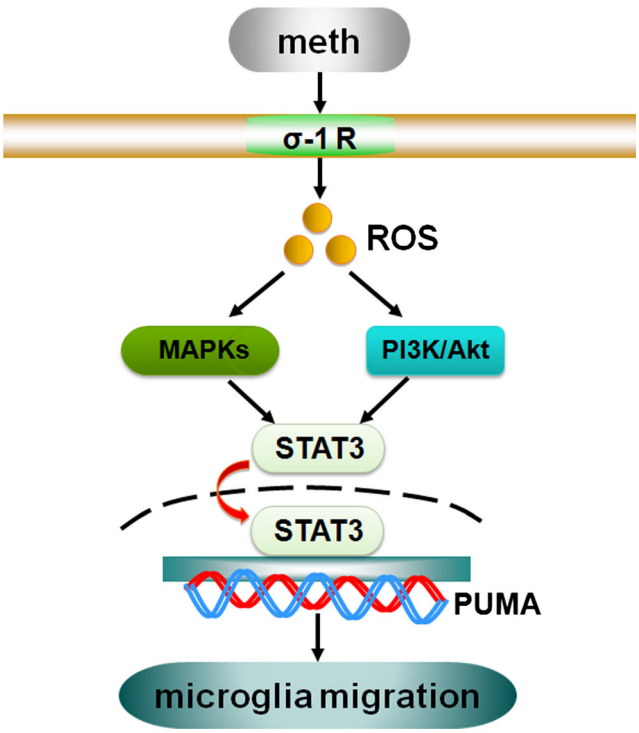

Fig. 6 Schematic of the signaling pathways involved in the methamphetamine-induced increased PUMA expression via sigma-1R, downstream activation of ROS and the MAPK and PI3K/Akt pathways and subsequent activation of STAT3, resulting in methamphetamine-induced microglial activation and migration. Meth, methamphetamine

Conclusion

In summary, our findings outlined the detailed molecular pathway involved in the methamphetamine-mediated migration of microglia via sigma-1R, which is involved in the downstream activation of ROS, JNK, p38 MAPK, PI3K/Akt pathways and the subsequent activation of STAT3, resulting in increased PUMA expression (Fig. 6). These findings provide insight into the migration of microglia by methamphetamine.

Acknowledgements This work was supported by grants from the National Natural Science Foundation of China (No. 81322048 and No. 81473190).

Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest.

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