Arsenic trioxide induces differentiation and apoptosis of malignant cells in vitro and in vivo, but the mechanisms by which such effects occur have not been elucidated. In the present study we provide evidence that arsenic trioxide induces activation of the small G-protein Rac1 and the α and β isoforms of the p38 mitogen-activated protein (MAP) kinase in several leukemia cell lines. Such activation of Rac1 and p38-isoforms results in downstream engagement of the MAP kinase-activated protein kinase-2 and is enhanced by pre-treatment of cells with ascorbic acid. Interestingly, pharmacological inhibition of p38 potentiates arsenic-dependent apoptosis and suppression of growth of leukemia cell lines, suggesting that this signaling cascade negatively regulates induction of antileukemic responses by arsenic trioxide. Consistent with this, overexpression of a dominant-negative p38 mutant (p38ΔAGF) enhances the antiproliferative effects of arsenic trioxide on target cells. To further define the relevance of activation of the Rac1/p38 MAP kinase pathway in the induction of arsenic-dependent antileukemic effects, studies were performed using bone marrows from patients with chronic myelogenous leukemia. Arsenic trioxide suppressed the growth of leukemic myeloid (CFU-GM) progenitors from such patients, whereas concomitant pharmacological inhibition of the p38 pathway enhanced its growth-suppressive effects. Altogether, these data provide evidence for a novel function of the p38 MAP kinase pathway, acting as a negative regulator of arsenic trioxide-induced apoptosis and inhibition of malignant cell growth.

Received for publication, July 17, 2002, and in revised form, September 5, 2002
Published, JBC Papers in Press, September 17, 2002, DOI 10.1074/jbc.M207176200

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Arsenic trioxide (As2O3) suppresses the growth of malignant cells in vitro and in vivo (1–4). Several studies have shown that this agent exhibits potent growth inhibitory effects on several cell lines of diverse malignant phenotypes, including leukemia, multiple myeloma, prostate carcinoma, and neuroblastoma cells (5–10). As2O3 exhibits its antineoplastic effects by inducing apoptosis and cell cycle arrest, whereas it also enhances differentiation of leukemia cells when used at lower doses (1–4). This agent is highly effective in the treatment of patients suffering from acute promyelocytic leukemia refractory to all-trans-retinoic acid, and this has made it an extremely important component in the clinical management of this leukemia (1–4). Despite the well documented clinical efficacy of arsenic in leukemia therapy, the precise mechanisms regulating arsenic-dependent induction of apoptosis of neoplastic cells have not been elucidated.

Mitogen-activated protein (MAP)1 kinases are a family of widely expressed serine-threonine kinases that regulate important cellular processes. Four MAPK family subgroups exist: extracellular signal-regulated kinases, c-Jun N-terminal or stress-activated protein kinases, extracellular signal-regulated kinase 5/big mitogen activated protein kinase 1 (BMK1), and the p38 group of protein kinases (reviewed in Ref. 11).

The family of p38 mitogen-activated protein kinases includes four known members, all of which are homologues of the HOG-1 MAP kinase in Saccharomyces cerevisiae (12–14). The different isoforms share significant structural homology with each other and include p38α (12–14), p38β (15–19), p38γ (20–22), and p38δ (23). The p38 family members exhibit serine kinase activities and upon their activation regulate phosphorylation/activation of other serine kinases, resulting in signals that mediate multiple biological responses. These include phosphorylation/activation of transcription factors (24, 25), as well as regulation of apoptosis (26–30). The p38 MAP kinase pathway mediates signals generated by various cellular stress stimuli, as well as signals generated by proinflammatory cytokines and hematopoietic growth factors (12–14, 31). There is also recent evidence that this pathway is activated by the Type I interferon receptor and plays a critical role in Type I IFN-dependent transcriptional activation and the induction of the biological effects of interferons (32–36). Recent studies from our laboratory (37) have shown that all-trans-retinoic acid (RA) induces activation of the p38 MAP kinase pathway and that pharmacological inhibition of p38 potentiates the antiproliferative and differentiating effects of RA on NB-4 cells (37). As arsenic trioxide suppresses the growth of acute promyelocytic leukemia cells in vitro, including

1 The abbreviations used are: MAP, mitogen-activated protein; MAPK, MAP kinase; MAPKapK-2, MAPK-activated protein kinase-2; RA, all-trans-retinoic acid; CML, chronic myelogenous leukemia; PBD, PAI1 binding domain; GST, glutathione S-transferase; CPU-GM, colony forming unit-granulocyte/macrophage; MTT, 3-(4,5-dimethyl-thiazol-2-yl)-2,5-diphenyltetrazolium bromide; HA, hemagglutinin.

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Fasting of the pharmacological inhibitors. Cell proliferation assays using the indicated doses of SB203580 and were subsequently treated with sample buffer. Proteins were subsequently analyzed by SDS-PAGE, 30 min at room temperature and was terminated by the addition of SDS kinase assays) and 25 Ci of \[\text{\text{[32P]ATP}}\], and 100 μM ATP, and resuspended in 30 μl of kinase buffer containing 5 μg GST-ATF2 (for the p38 kinase assays) or 5 μg of hsp25 protein (for the MAPKapK-2 kinase assay) (40 μM of \(\text{\text{[32P]ATP}}\)). The reaction was incubated for 30 min at room temperature and was terminated by the addition of SDS sample buffer. Proteins were subsequently analyzed by SDS-PAGE, and the phosphorylated forms of ATF2 or hsp25 were detected by autoradiography.

Cell Proliferation Assays—NB-4 cells were pre-treated for 30–60 min with the indicated doses of SB203580 and were subsequently treated with or without the indicated doses of arsenic trioxide for the indicated times in the continuous presence of the pharmacological inhibitors. Cell proliferation assays using the MTT method were performed as in previous studies (35, 42).

Hematopoietic Progenitor Cell Assays—The effects of arsenic trioxide on the growth of hematopoietic progenitors from patients with CML was determined in clonogenic assays in methylcellulose, as in previous studies (35, 36, 43). Bone marrow aspirate specimens were obtained under local anesthesia from patients with chronic myelogenous leukemia, after obtaining informed consent approved by the Institutional Review Board of the University of Illinois at Chicago. Bone marrow mononuclear cells were separated by Ficoll Hypaque sedimentation, and cells were cultured in a methylcellulose mixture containing hematopoietic growth factors (35, 36, 43), in the presence or absence of arsenic trioxide (2 μM) and SB203580 (5 or 10 μM). Colony forming units-granulocyte/macrophage (CFU-GM) from the leukemic bone marrows were scored on day 14 of culture.

Evaluation of Apoptosis—Cell lines were exposed to arsenic trioxide in the presence or absence of SB203580 (10 μM) as indicated. The caspase activity of apoptotic cells was determined by flow cytometry after staining with fluorescein-conjugated annexin-V and propidium iodide, as in previous studies (36, 44).

We first determined whether ArsO3 treatment induces phosphorylation/activation of the p38 (also called p38α) MAP kinase in NB-4 acute promyelocytic leukemia cell line. NB-4 cells were incubated for 30 or 60 min in the presence or absence of ArsO3. The cells were subsequently lysed in phosphorylation lysis buffer, and total lysates were resolved by SDS-PAGE and immunoblotted with an antibody against the phosphorylated/activated form of p38. ArsO3 treatment induced strong phosphorylation of p38 after either 30 or 60 min of treatment (Fig. 1A). Such phosphorylation of p38 was detectable when low (0.5 μM) or high (2 μM) doses of ArsO3 were used (Fig. 1A). Stripping and reprobing the blots demonstrated that equal amounts of p38 were detectable prior to and after ArsO3 treatment (Fig. 1B). We subsequently determined whether arsenic-dependent phosphorylation/activation of p38 (p38Ars) occurs in an NB-4 variant cell line, NB-4.007/6 (38). This variant form of NB-4 is refractory to all-trans-RA-induced differentiation and inhibition of cell growth, because of constitutive degradation of PML-RAR (38), and in our previous studies we have shown that the activation of p38 by all-trans-retinoic acid is defective in these cells (37). Treatment of NB-4.007/6 cells with ArsO3 resulted in phosphorylation of p38 (Fig. 1C and D), consistent with the fact that these cells are responsive to the growth inhibitory effects of ArsO3 (data not shown). Thus, ArsO3 induces phosphorylation of p38 in cells that are resistant to the growth inhibitory effects of RA, indicating that the early upstream regulatory signals that mediate ArsO3-dependent activation of p38 are different from the ones mediating RA-dependent activation. The activation of p38 by ArsO3 in NB-4 cells was sustained and prolonged and could be detected for as long as 4 days of ArsO3 treatment of the cells, a time point at which ArsO3 induces cell-differentiation (Fig. 1E).

In parallel studies, we examined whether the β-isofrom of p38 (p38β) is expressed in acute promyelocytic leukemia cells and whether ArsO3 induces its activation. NB-4 cells were incubated in the presence or absence of ArsO3, and after cell lysis, cell lysates were immunoprecipitated with a specific anti-
p38β antibody. Immune-complex kinase assays were subsequently carried out on the immunoprecipitates, using ATP2 as an exogenous substrate. As shown in Fig. 2B, treatment of the cells with As2O3 resulted in induction of the kinase activity of p38β, evidenced by the phosphorylation of ATP2 used as an exogenous substrate (Fig. 2A). Thus, in addition to the p38α, the p38β isoform is also activated by As2O3 in the NB-4 acute promyelocytic leukemia cell line, suggesting that it also participates in the induction of As2O3 responses in these cells.

Previous studies have established that a downstream effector for p38 is the MAPKapK-2 kinase, which is activated in response to stress signals and growth factors (31, 45), as well as in response to interferon-dependent activation of the p38 pathway (33, 35). We examined whether As2O3-induced activation of p38 leads to downstream engagement and activation of MAPKapK-2 in NB-4 cells. Cells were incubated in the presence or absence of As2O3, lysates were immunoprecipitated with an anti-MAPKapK-2 antibody, and immunoprecipitated proteins were subjected to in vitro kinase assays using hsp25 as an exogenous substrate. As2O3 treatment of the cells resulted in activation of MAPKapK-2, evidenced by the phosphorylation of hsp25 in the kinase assay (Fig. 2B). In addition, pre-treatment of cells with the p38-specific inhibitor SB203580 completely abrogated the As2O3-inducible activation of MAPKapK-2 (Fig. 2B), demonstrating that the engagement of MAPKapK-2 in an As2O3-dependent cellular pathway occurs downstream of p38.

In addition to its effects against acute promyelocytic leukemia cells, As2O3 has been shown to exhibit pro-apoptotic and growth inhibitory effects in a variety of different tumor cell lines (5–10). To examine whether activation of the p38 pathway by arsenic is limited to cells of promyelocytic origin or also occurs in cells of other malignant phenotypes, the phosphorylation/activation of p38 was examined in several cell lines of diverse origin. The cell lines used included the K562 acute erythroleukemia cell line, which has been derived from a patient with CML in blast crisis and expresses BCR-ABL, the LNKAP prostate carcinoma cell line, and the MCF-7 breast carcinoma cell line, all of which exhibited sensitivity to the growth inhibitory effects of As2O3 in MTT cell proliferation assays (data not shown). As shown in Fig. 3, As2O3 induced strong phosphorylation/activation of p38 in K562 cells (Fig. 3, A and B), LNKAP cells (Fig. 3, C and D), and MCF-7 cells (Fig. 3, E and F). Thus, the p38-pathway is activated in an As2O3-dependent manner in a variety of malignant cell phenotypes, indicating that it plays a universal role in the generation of As2O3 responses.

It is well established that the activated, GTP-bound form of the small G-protein Rac1 acts as an upstream regulator of the p38 MAP kinase pathway in response to various stimuli (33, 35, 37, 46–48). We examined whether As2O3 induces activation of Rac1 to regulate downstream engagement of p38 in NB-4 cells. As2O3 treatment resulted in activation of Rac1, as shown by the increase in the GTP-bound form of Rac1 (Fig. 4A), providing the first evidence for engagement of this small G-protein in an As2O3-activated cellular pathway, and strongly suggesting that this GTPase is an upstream regulator of the As2O3-dependent activation of p38. To better understand the mechanisms of activation of the Rac1/p38 pathway by As2O3, we examined whether the activation of Rac1 is downstream or upstream of the redox reactions and free radicals generated by arsenic trioxide treatment. Previous studies have shown that ascorbic acid enhances As2O3-mediated responses, by increasing cellular H2O2 stores (49, 50). We therefore determined the effects of ascorbic acid on the As2O3-dependent activation of Rac1. When cells were pretreated with ascorbic acid prior to As2O3 treatment, there was an increase in the As2O3-induced.
As2O3-induced apoptosis. NB-4 cells were incubated with arsenic trioxide for 2 days, in the presence or absence of SB203580, and the percentage of cells undergoing apoptosis was determined by flow cytometry. Treatment of cells with SB203580 alone did not alter the percent of background apoptotic cells compared with untreated cells (Fig. 6). As expected (50), treatment of cells with As2O3 resulted in strong induction of apoptosis (Fig. 6), whereas concomitant treatment of cells with the p38 inhibitor further enhanced As2O3-induced cell death (Fig. 6).

Altogether, the findings using the SB203580 pharmacological inhibitor of p38 strongly suggested that this pathway exhibits a negative regulatory role on As2O3-induced apoptosis. To confirm that this is indeed the case, we determined whether overexpression of a phosphorylation-defective mutant (p38β2AGF) exhibits dominant-negative effects on arsenic-induced cell death. We first generated the pCDN-p38β2AGF mutant, in which threonine 180 and tyrosine 182 in the TGT motif of p38β were mutated to arginine and phenylalanine, respectively, rendering the mutant resistant to dual threonine-tyrosine phosphorylation and activation by upstream MAP kinases. MCF-7 cells were subsequently transfected with either the empty pCDN vector or the pCDN-p38β2AGF mutant tagged with HA, and the transfectants were selected in G418. Prior to examining the effects of overexpression of this mutant on As2O3-dependent apoptosis, the expression of the p38β2AGF protein and its ability to block endogenous p38β activation were examined. The p38β2AGF mutant was expressed abundantly in the transfectants (Fig. 7A), as shown by anti-HA immunoblots. In addition, overexpression of the p38β2AGF mutant blocked endogenous p38β kinase activation in response to arsenic trioxide stimulation, whereas...
such activation was intact in cells transfected with the empty pCDN vector (Fig. 7B). In a similar manner, the activation of the MAPKapK-2 kinase downstream of p38 was intact in cells transfected with the empty vector (Fig. 7C) but defective in the p38\textsuperscript{H9252}AGF transfectants (Fig. 7D).

Subsequently, experiments were performed in which the growth inhibitory effects of arsenic trioxide were examined in MCF-7 cells stably transfected with either the empty pCDN vector or the HA-tagged pCDN-p38\textsuperscript{H9252}AGF construct were lysed, and total cell lysates were analyzed by SDS-PAGE and immunoblotted with an anti-HA antibody. B, MCF-7 cells stably transfected with either the empty pCDN vector or the pCDN-p38\textsuperscript{H9252}AGF construct were treated with As\textsubscript{2}O\textsubscript{3} as indicated, and cell lysates were immunoprecipitated with an anti-p38 antibody. Immunoprecipitates were subjected to an in vitro kinase assay, using hsp25 as an exogenous substrate. Proteins were resolved by SDS-PAGE, and phosphorylated proteins were detected by autoradiography.

and further support a role for p38 as a negative regulator of arsenic-induced apoptosis.

To further explore the role of the p38 pathway in a more physiologically relevant system, we evaluated the effects of pharmacological inhibition of p38 on the induction of the suppressive effects of arsenic trioxide on primary leukemia progenitors from patients with CML. Bone marrow mononuclear cells from three patients with CML were isolated, and leukemic CFU-GM progenitor colony formation was determined by clonogenic assays in methylcellulose. Addition of As\textsubscript{2}O\textsubscript{3} to the cultures suppressed leukemic progenitor growth from the bone marrows of all three cases studied (Fig. 9), whereas addition of the SB203580 p38 inhibitor alone had no significant effects.
However, SB203580 further enhanced the suppressive effects of As$_2$O$_3$ on leukemic CFU-GM (Fig. 9), demonstrating that activation of p38 exhibits negative regulatory effects on the leukemic progenitor cell growth suppression by arsenic trioxide.

**DISCUSSION**

Arsenic trioxide induces apoptosis of target cells and exhibits growth inhibitory effects against a variety of human cell lines in vitro and in vivo. The important properties that this agent exhibits against leukemia and other malignant cells have led to extensive studies, aimed to understand the mechanisms by which it mediates its effects. There is evidence that this compound induces cell cycle arrest, apoptosis, and/or differentiation of target cells, depending on the doses used and the cellular context (1–4, 8, 52). Previous studies have provided evidence for several mechanisms that may be contributing to arsenic-induced apoptosis. It has been demonstrated that, in acute promyelocytic leukemia cells, arsenic trioxide lowers bcl-2 levels and reduces NF-$\kappa$B translocation to the nucleus, whereas it also induces collapse of mitochondrial transmembrane potential, resulting in cytochrome c release and activation of caspase-3 (53, 54). All these events appear to contribute to the induction of apoptosis, but the upstream regulatory mechanisms of such pro-apoptotic signals are not known. Interestingly, generation of reactive oxygen species by arsenic trioxide potentiates induction of cell killing (8, 50), and an
accumulating body of evidence points toward an important role of reactive oxygen species, particularly H$_2$O$_2$, on arsenic-induced apoptosis (55). Generation of H$_2$O$_2$ is dependent on cellular glutathione stores, whereas reduced cellular glutathione (GSH) acts as an inhibitor of arsenic-dependent cell death, by either conjugating arsenic in the form of As(GSH)$_2$ complexes or by sequestering the reactive oxygen species induced by arsenic (55). This has prompted studies aimed to determine whether depletion of intracellular GSH stores can enhance the effects of arsenic. Such studies have demonstrated that down-regulation of GSH levels by pre-treatment of myeloma cells with either ascorbic acid (55) or buthionine sulfoximine (5) promotes induction of arsenic-dependent apoptosis. On the other hand, increasing GSH cellular levels by pre-treatment with N-acetylcysteine attenuates arsenic-dependent cytotoxicity (55).

Altogether, these studies have established that induction of apoptotic signals by arsenic trioxide is dependent on the generation of reactive-oxygen species and the cellular redox system. However, it is not known whether during treatment of cells with arsenic trioxide other cellular pathways are activated in a negative-feedback manner. Induction of such cellular signals might counteract arsenic-activated cascades that mediate apoptosis and provide a mechanism by which malignant cells develop resistance to its pro-apoptotic properties. We have demonstrated recently that during differentiation of acute promyelocytic leukemia cell lines in response to all-trans-retinoic acid, there is activation of the p38 MAP kinase pathway (37). This pathway apparently exhibits negative regulatory effects on the induction of cell differentiation and growth inhibition by all-trans-retinoic acid (37), as pharmacological inhibitors of p38 strongly enhance all-trans-retinoic acid-dependent differentiation and growth suppression of acute promyelocytic leukemia cells (37). As arsenic trioxide is a potent inducer of apoptosis of acute promyelocytic leukemia cells, including all-trans-retinoic acid-resistant cells, we performed studies to examine whether it elicits activation of the p38 pathway in acute promyelocytic leukemia. Our studies provide the first evidence that arsenic trioxide activates the $\alpha$ and $\beta$ isomers of the p38 MAP kinase in acute promyelocytic leukemia cells. Such activation was detectable in both the NB-4 acute promyelocytic leukemia cell line and in an all-trans-retinoic acid-resistant NB-4 variant (NB-4.007/6) (38). This is of particular interest, as retinoic acid does not activate the p38 pathway in NB-4.007/6 cells, indicating that different early signals mediate arsenic-induced p38 activation, as compared with retinoic acid-dependent activation. In other experiments we demonstrated that p38 is activated during treatment of other cell lines of diverse malignant phenotypes with arsenic, indicating that arsenic-dependent activation of this cascade is not cell-type restricted. Our data also demonstrate that the small GTPase Rac1 is activated by arsenic and that the activation of p38 ultimately leads to engagement and activation of the MAPKap2-kinase, which functions as a downstream effector for the p38-pathway. Interestingly, activation of Rac1 and p38 by arsenic was enhanced by pre-treatment of cells with ascorbic acid and was blocked by dithiothreitol, indicating that GSH levels exhibit regulatory effects on its activation.

Altogether, our studies indicate that treatment of cells with arsenic results in sequential activation of a Rac1 $\rightarrow$ (M KK) $\rightarrow$ p38(\alpha/\beta) $\rightarrow$ MAPKap2-kinase cascade, whose activation is probably downstream of cellular redox changes induced by arsenic. In experiments to define the functional role of this pathway in the induction of arsenic responses we found that inhibition of this cascade enhances arsenic-dependent induction of apoptosis and suppression of cell growth of arsenic-responsive cell lines. This was demonstrated by experiments using SB203580, a specific pharmacological inhibitor of p38, which acts by binding to the ATP site of the molecule to abrogate its kinase activity. The basis of the specificity of this pharmacological inhibitor of p38 has been established previously by mutagenesis studies and x-ray crystallographic structures of p38-inhibitor complexes (56–58). Previous studies have also demonstrated that this pyridinyl imidazole compound blocks activation of both the p38$\alpha$ and p38$\beta$ isoforms, which, based on our data, are both activated during arsenic trioxide treatment of target cells but not the p38$\gamma$ and p38$\delta$ isoforms of p38. Consistent with this, we were able to demonstrate that overexpression of a phosphorylation-defective p38$\gamma$ isomutant enhances arsenic-dependent cytotoxicity in MCF-7 cells, confirming the data with the pharmacological inhibitor of p38.

The observation that the combination of arsenic trioxide and SB203580 has more potent cytotoxic effects than arsenic alone in vitro raises the possibility that such combination may result in more potent antileukemic effects in vivo. In addition to acute promyelocytic leukemia, another leukemia in which such combination may prove to be of therapeutic value is CML.

CML is a clonal myeloproliferative disorder of stem cells, characterized by the expression of the BCR-ABL oncoprotein. The BCR-ABL abnormal protein is the product of the bcr-abl oncogene, which is generated by the reciprocal translocation between chromosomes 9 and 22, resulting in the fusion of bcr to c-abl (60–62). The function of the abnormal BCR-ABL tyrosine kinase is essential for the pathogenesis of CML (63) by mediating mitogenic effects via phosphorylation of protein substrates and activation of multiple downstream mitogenic pathways (64). Studies from other groups have demonstrated previously that arsenic trioxide induces apoptosis of BCR-ABL-expressing cell lines (65). Interestingly, arsenic trioxide-induced apoptosis of such cell lines was associated with a decrease in the levels of the BCR-ABL oncoprotein but no significant effects in the levels of Bel-2, Bax, Apaf-1, Fas, and FasL (65). Other studies have suggested that arsenic trioxide may have selective inhibitory effects on the proliferation of BCR-ABL-expressing cells, as it was found to induce apoptosis of Ph$^+$ but not Ph$^-$ lymphoblasts, whereas ectopic expression of BCR-ABL in U937 myelomonocytic cells dramatically increased their sensitivity to arsenic trioxide, independently of BCR-ABL kinase activity (66). Also, arsenic trioxide has been shown previously to reduce proliferation of CML leukemic blasts (66). Our data are consistent with these findings, as they demonstrate that arsenic trioxide suppresses leukemic CFU-GM colony formation from CML bone marrows. Most importantly, they demonstrate that such effects can be enhanced by p38 inhibition, raising the possibility that p38 inhibitors may enhance the clinical activity of arsenic trioxide. This may prove to be important in the design of future therapeutic approaches in the treatment of CML, where studies with arsenic are being planned or are already in progress (51, 67, 68).

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Activation of Rac1 and the p38 Mitogen-activated Protein Kinase Pathway in Response to Arsenic Trioxide

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J. Biol. Chem. 2002, 277:44988-44995.
doi: 10.1074/jbc.M207176200 originally published online September 17, 2002

Access the most updated version of this article at doi: 10.1074/jbc.M207176200

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