Arsenite-induced Phosphorylation of Histone H3 at Serine 10 Is Mediated by Akt1, Extracellular Signal-regulated Kinase 2, and p90 Ribosomal S6 Kinase 2 but Not Mitogen- and Stress-activated Protein Kinase 1*

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Arsenite is known to be an environmental human carcinogen. However, the mechanism of action of this compound in skin carcinogenesis is not completely clear. Here, we provide evidence that arsenite can induce phosphorylation of histone H3 at serine 10 in a time- and dose-dependent manner in JB6 Cl 41 cells. Arsenite induces phosphorylation of Akt1 at serine 473 and increases Akt1 activity. A dominant-negative mutant of Akt1 inhibits the arsenite-induced phosphorylation of histone H3 at serine 10. Additionally, active Akt1 kinase strongly phosphorylates histone H3 at serine 10 in vitro. The arsenite-induced phosphorylation of histone H3 at serine 10 was almost completely blocked by a dominant-negative mutant of extracellular signal-regulated kinase 2 and the mitogen-activated protein kinase/extracellular signal-regulated kinase inhibitor PD98059. A C-terminal mutant mitogen- and stress-activated protein kinase 1 or its inhibitor I299 had no effect on arsenite-induced phosphorylation of histone H3 at serine 10 in JB6 Cl 41 cells. However, cells deficient in p90 ribosomal S6 kinase 2 (Rsk2<sup>−/−</sup>) totally block this phosphorylation in a dose- and time-dependent manner. Taken together, these results suggest that arsenite-induced phosphorylation of histone H3 at serine 10 is mediated by Akt1, extracellular signal-regulated kinase 2 and p90 ribosomal S6 kinase 2 but not mitogen- and stress-activated protein kinase 1.

1 The abbreviations used are: MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; MEM, minimal essential medium (MEM), RPMI 1640 medium, l-glutamine, and LipofectAMINE<sup>TM</sup> 2000 reagent were from Invitrogen. Plasmids of pCMV5-FLAG vector, pCMV5-FLAG-wild-type MSK1, pCMV-FLAG-MSK1 A195-N-terminal kinase-dead, and pCMV5-FLAG-MSK1 A565/C-terminal kinase-dead were kindly provided by Dr. D. Alessi (MRC Protein Phosphorylation Unit, Dundee, Scotland, UK). Antibodies to detect phosphorylation of histone H3 at serine 10 and total histone H3 protein, phosphorylation of MSK1 and RSK2, dominant-negative (DN)-Akt1 and activated-Akt1 plasmid, and pure histone H3 protein were systems (10). On the other hand, arsenite is also an extremely effective chemotherapeutic agent used to treat certain cancer patients, especially those with acute promyelocytic leukemia (11, 12). Studies show that arsenite can induce apoptosis in many cell types because of its ability to increase activation of the tumor suppressor protein p53 (13). The ability of arsenic to act as either a carcinogen or a chemotherapeutic agent is related to cell type, arsenic species, and length and dose of exposure (1). Thus, arsenic acts in a paradoxical manner. However, the mechanisms of arsenic’s actions as a carcinogen or as a chemotherapeutic agent are unclear.

Phosphorylation of histone H3 is known to play an important role in chromatin remodeling and chromosome condensation (14). Phosphorylation of histone H3 is associated with active immediate-early gene expression, including that of proto-oncogenes c-fos and c-jun (15, 16). We reported that UVB-induced phosphorylation of histone H3 at serine 10 is mediated by MAPKs (17). However, the ability of arsenite to induce phosphorylation of histone H3 at serine 10 has not been reported, and the signal transduction pathway mediating phosphorylation of histone H3 at serine 10 also remains unclear.

To explore the mechanism of arsenite’s action in carcinogenesis, we used arsenite to induce phosphorylation of histone H3 at serine 10 in JB6 Cl 41 cells. We found that this compound induced phosphorylation of histone H3 at serine 10 in a time- and dose-dependent manner and increased Akt1 activation and phosphorylation of Akt1 at serine 473. A dominant-negative mutant of Akt1 inhibited phosphorylation of histone H3 at serine 10, and a dominant-negative mutant of ERKs and the ERK inhibitor PD98059 also blocked the phosphorylation of histone H3 at serine 10. In addition, arsenite-induced phosphorylation of histone H3 at serine 10 was totally blocked in ribosomal S6 protein kinase 2 (Rsk2<sup>−/−</sup>)-deficient cells (Rsk2<sup>−/−</sup>). Furthermore, dominant-negative mutant MSK1 had no effect on phosphorylation of histone H3 at serine 10 induced by arsenite. Taken together, these data indicate that Akt1, ERKs, and RSK2, but not MSK1, are involved in the mediation of arsenite-induced phosphorylation of histone H3 at serine 10.

EXPERIMENTAL PROCEDURES

Materials—Sodium arsenite was purchased from Merck (Darmstadt, Germany). Lowry-modified reagent was from Sigma. Eagle’s minimal essential medium (MEM), RPMI 1640 medium, l-glutamine, and LipofectAMINE<sup>TM</sup> 2000 reagent were from Invitrogen. Plasmids of pCMV5-FLAG vector, pCMV5-FLAG-wild-type MSK1, pCMV-FLAG-MSK1 A195-N-terminal kinase-dead, and pCMV5-FLAG-MSK1 A565/C-terminal kinase-dead were kindly provided by Dr. D. Alessi (MRC Protein Phosphorylation Unit, Dundee, Scotland, UK). Antibodies to detect phosphorylation of histone H3 at serine 10 and total histone H3 protein, phosphorylation of MSK1 and RSK2, dominant-negative (DN)-Akt1 and activated-Akt1 plasmid, and pure histone H3 protein were

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from Upstate Biotechnology (Lake Placid, NY). Fetal bovine serum (FBS) was from Gemini Bio-Product (Calabasas, CA). Gentamicin sulfate was from Cambrex Bio Science Walkersville, Inc. (Herndon, VA). The Akt1 Kinase Assay Kit was from Cell Signaling Technology, Inc. (Beverly, MA). Folin & Ciocalteu’s phenol reagent was from Pierce, and polyvinylidine difluoride membrane was from Millipore (Bedford, MA).

**Cell Culture**—The JB6 mouse epidermal cell line Cl 41, DN-Akt1 and activated-Akt1 plasmid stably transfected JB6 cells, DN-ERK2 plasmid stably transfected JB6 cells, and N-terminal mutant MSK1, wild-type MSK1, and C-terminal mutant MSK1 plasmid stably transfected JB6 cells were cultured as adherent monolayers in MEM supplemented with 5% (v/v) heat-inactivated FBS, and 2 mM glutamine at 37 °C in a humidified atmosphere of 5% CO2. 

**Establishing the Stably Transfected JB6 Cells**—Using plasmids pCMV5-FLAG vector, pCMV5-FLAG-wild-type MSK1, pCMV-FLAG-MSK1 A195S-N-terminal kinase-dead, pCMV5-FLAG-MSK1-A565/C-terminal kinase-dead, DN-ERK2, DN-Akt1, and activated-Akt1, we established these stable transfections according to the protocol from Upstate Biotechnology. Briefly, cells were scraped from the plates after treatment and centrifuged at 1000 rpm at 4 °C for 4 min. Cells were washed once with PBS and resuspended with 10 volumes of lysis buffer (10 mM HEPES, pH 7.9, 1.5 mM MgCl2, 10 mM KCl, 1.5 mM phenylmethylsulfonyl fluoride, and 0.5 mM dithiothreitol) and then sulfuric acid (H2SO4 for 30 min) was added to a final concentration of 0.2 M and extractions were left on ice. Extraction solutions were centrifuged at 15,000 rpm for 10 min at 4 °C, and the acid-insoluble pellets were discarded. Supernatant fractions were transferred to fresh tubes and precipitated on ice for 45 min with a final concentration of 20% trichloroacetic acid. Samples were then centrifuged at 14,000 rpm for 10 min at 4 °C, and the pellets were washed once with 0.1% acetic acid and once with pure acetone. Acid-soluble proteins were dissolved in 0.1 N NaOH solution and stored at −20 °C.

**Assay of Acid-soluble Proteins**—After arsenite treatment, cells were harvested and washed twice with phosphate-buffered saline (PBS). Extraction of the acid-soluble proteins was performed according to the protocol described by Upstate Biotechnology. Briefly, cells were scraped from the plates after treatment and centrifuged at 1000 rpm at 4 °C for 4 °C. The pellets were suspended in 40 μl of GSK-3 fusion protein and incubated for 30 min at 30 °C (59 °C) before they were separated by 8% SDS-PAGE. The proteins were transferred to polyvinylidine difluoride membranes. Akt1 kinase activity and Akt1 phosphorylation were analyzed by Western blotting using a phospho-Akt1 (serine 473) antibody and a phosphor-Akt1 (serine 21/9) antibody and a phospho-Akt1 (serine 21/9) antibody.

**Protein Phosphorylation Assay in Vitro**—Phosphorylation of pure histone H3 at serine 10 by Akt1, ERK2, and RSK2

**Phosphorylation of Histone H3 at Serine 10 by Akt1, ERK2, and RSK2**

**Arsenite Induces Phosphorylation of Histone H3 at Serine 10**—Acid-soluble proteins were dissolved in SDS sample buffer and separated by 15% SDS-PAGE and then transferred to polyvinylidine difluoride membranes. Membranes were blocked with 5% nonfat dry milk in PBS for 1 h at room temperature and incubated overnight at 4 °C with the primary antibody against phosphorylation of histone H3 at serine 10, acetylation of histone H3 at lysine 9, or total histone H3. These membranes were incubated for another 4 h at 4 °C with secondary antibodies against rabbit IgG-conjugated alkaline phosphatase. Membrane-bound proteins were detected with enzyme-catalyzed fluorescence (Amersham Biosciences) and analyzed using the Storm 840 PhosphorImager (Amersham Biosciences). 

**Establishing the Stably Transfected JB6 Cells**—Using plasmids pCMV5-FLAG vector, pCMV5-FLAG-wild-type MSK1, pCMV5-FLAG-MSK1 A195S-N-terminal kinase-dead, pCMV5-FLAG-MSK1-A565/C-terminal kinase-dead, DN-ERK2, DN-Akt1, and activated-Akt1, we established these stable transfections according to the protocol from Upstate Biotechnology. All of these cells were selected in media containing 400 μg/ml G418 for 2 weeks; the G418 concentration was then decreased to 200 μg/ml and maintained. Control cells were transfected with pCMV5-FLAG neo only (“mock”). G418-selected cells were tested for FLAG-epitope-tagged Msk1 by indirect immunofluorescence staining with a monoclonal FLAG antibody or by kinase assay for Akt1.

**Akt1 Kinase Assay**—The ability of arsenite to induce phosphorylation of Akt1 was tested using an Akt1 kinase assay kit. In brief, cells were treated with arsenite at various concentrations for desired times. Cells were washed once with ice-cold PBS after removing the media, and then 0.5 ml of 1× ice-cold cell lysis buffer plus 1× phenylmethylsulfonyl fluoride was added to each plate and kept on ice for 5 min, scraped, and transferred to fresh tubes. Cells were sonicated on ice four times for 5 s each and centrifuged for 10 min at 4 °C, and the supernatant fractions were transferred to other fresh tubes. Cell lysate protein (200 μg) and beads (20 μl) with immobilized Akt1 1G1 monoclonal antibody were added together by gently rocking for 2 h at 4 °C. These tubes were centrifuged at 30 °C at 4 °C, washed twice with 500 μl of 1× cell lysis buffer, and then washed twice with 500 μl of 1× kinase buffer. The pellets were suspended in 40 μl of 1× kinase buffer supplemented with 200 μM ATP and 2 μg of GSK-3 fusion protein and incubated for 30 min at 30 °C. The reaction was terminated with 20 μl of 3× SDS sample buffer. The samples were denatured at 95–100 °C for 5 min before they were separated by 8% SDS-PAGE. The proteins were transferred to polyvinylidine difluoride membranes. Akt1 kinase activity and Akt1 phosphorylation were analyzed by Western blotting using a phospho-GSK-3α/β at serine 21/9 antibody and a phospho-Akt1 (serine 473) antibody, respectively.

**Results**

**Arsenite Induces Phosphorylation of Histone H3 at Serine 10 in a Time- and Dose-dependent Manner**—JB6 Cl 41 cells were employed to analyze the arsenite-induced phosphorylation of histone H3 at serine 10. The time-response study indicates that phosphorylation of histone H3 at serine 10 gradually increases from 15 min to 1 h after treatment with arsenite (10 μM) (Fig. 1, A and B). The level of total histone H3 protein did not change.

**Fig. 1. Arsenite induces phosphorylation of histone H3 at serine 10 in a dose-dependent manner.** JB6 Cl 41 cells were starved for 48 h in 0.1% FBS/MEM at 37 °C in a 5% CO2 atmosphere. Cells were then incubated in fresh 0.1% FBS/MEM for another 2 h before being treated with arsenite (10 μM) for the indicated time periods. Acidic proteins were extracted as described under “Experimental Procedures.” Using Western blot analysis, phosphorylation of histone H3 at serine 10 was detected (A) and analyzed (B) using the Storm PhosphorImager analysis system (Amersham Biosciences). Total histone H3 protein (C) was determined as described under “Experimental Procedures.”
(Fig. 1C). The dose course study shows that phosphorylation of histone H3 gradually increases after treatment with increasing amounts of arsenite (1, 5, or 10 μM) (Fig. 2, A and B), with no effect on total histone H3 protein levels (Fig. 2C). These results indicate that phosphorylation of histone H3 at serine 10 is induced by arsenite in a dose- and time-dependent manner.

**Arsenite Increases Akt1 Kinase Activity and Phosphorylation of Akt1 at Serine 473 in JB6 Cl 41 Cells—**Akt1 kinase activity was analyzed by Western blotting using a specific antibody against phosphorylation of GSK3β, which is a target of Akt1 kinase. Our results show that arsenite induced phosphorylation of GSK3β via activation of Akt1 kinase (Fig. 3, A and B) without changing the total GSK3 protein level (Fig. 3C). In addition, we found that arsenite induced phosphorylation of Akt1 at serine 473 (Fig. 3D), whereas the non-phosphorylated level of Akt1 was unchanged (Fig. 3E).

**DN Mutant Akt1 Inhibits Phosphorylation of Histone H3 at Serine 10—**To further explore the role of Akt1 in arsenite-induced phosphorylation of histone H3 at serine 10, we established stably expressed DN-Akt1, activated-Akt1, and empty vector plasmid-transfected JB6 cells. Our data show that phosphorylation of histone H3 at serine 10 induced by arsenite was still observed in all of the stably transfected cells (Fig. 4, A and C). However, DN-Akt1 distinctly inhibited phosphorylation of histone H3 (serine 10) compared with the empty vector-transfected cells (Fig. 4, A and C). The non-phosphorylated levels of histone H3 proteins remained at the same level (Fig. 4, B and D). Moreover, the phosphorylation of histone H3 (serine 10) was also dose-dependent in all cell lines (Fig. 4C). These results indicate that Akt1 plays a very important role in mediating the phosphorylation of histone H3 at serine 10 induced by arsenite.

**Active Akt1 Phosphorylates Histone H3 at Serine 10 In Vitro—**Furthermore, we wanted to know whether Akt1 kinase can directly phosphorylate histone H3 at serine 10 in vitro. We used pure histone H3 protein or chromatin extracted from JB6 cells.
Phosphorylation of Histone H3 at Serine 10 by Akt1, ERK2, and RSK2

Dominant-Negative Mutant ERK2 and PD98059 Inhibit Phosphorylation of Histone H3 at Serine 10 Induced by Arsenite—In DN-ERK2 plasmid-transfected cells compared with empty vector plasmid-transfected cells, we found that DN-ERK2 almost completely blocks the phosphorylation of histone H3 at serine 10 (Fig. 6A), but the expression level of non-phosphorylated histone H3 at serine 10 (Fig. 6A) and chromatin (Fig. 5C) was unchanged. These data indicate that Akt1 can phosphorylate histone H3 protein at serine 10 of chromatin in vitro.

Mutants of MSK1 and the MSK1 Inhibitor H89 Have no Effect on Arsenite-induced Phosphorylation of Histone H3 at Serine 10—MSK1 has already been reported to be a mediator in the phosphorylation of histone H3 at serine 10 by the Ras-MAPK signal transduction pathway (14). In this study, we first determined whether DN-MSK1 inhibited UVB-induced phosphorylation of histone H3 at serine 10. Our data corresponded with that of previous studies (18) and indicated that N- and C-terminal kinase dead plasmid-transfected JB6 Cl 41 cells were starved in 0.1% FBS/MEM for 48 h and then treated with UVB (4 kJ/m² as a positive control) or arsenite. Phosphorylation of histone H3 at serine 10 (A, C, and F), acetylation of histone H3 at lysine 9 (D and G), and total histone H3 (B, E, and H) were detected with the corresponding specific antibodies. JB6 Cl 41 cells were pretreated with H89 for 1 h and then treated with arsenite (10 μM) or arsenite for an additional 1 h. The phosphorylation of histone H3 at serine 10 (I and J) and total histone H3 (J) were detected as above.

RSK2-deficient Cells Block Arsenite-induced Phosphorylation of Histone H3 at Serine 10—Reports indicate that RSK2 is another very important factor in mediating phosphorylation of histone H3 (19). In the present report, Rsk2-deficient cells were

![Image](https://example.com/image.png)
Phosphorylation of Histone H3 at Serine 10 by Akt1, ERK2, and RSK2

**DISCUSSION**

Studies show that JB6 Cl 41 cells, which are derived from mouse skin, are a well developed cell culture model for studying tumor promotion (20, 21). Moreover, we found previously that exposure of JB6 P+ cells to low concentrations of arsenic induces cell transformation (22). In the present study, to further explore the mechanism of arsenic’s action in carcinogenesis, JB6 Cl 41 cells were employed to study phosphorylation of histone H3 at serine 10 induced by arsenic. Using dominant-negative mutant cells and kinase inhibitors, we found that arsenic-induced phosphorylation of histone H3 at serine 10 is blocked almost completely by arsenic-induced phosphorylation of histone H3 at serine 10 in a time- and dose-dependent manner (Figs. 8, A, and D), with no effect on protein expression of non-phosphorylated histone H3 or acetylation of histone H3 at lysine 9 (Fig. 8, B, C, E, and F). This result indicates that RSK2 also takes part in the mediation of arsenic-induced phosphorylation of histone H3 at serine 10.

Unlike UVB-induced phosphorylation of histone H3 at serine 28, which is mediated through MSK1, arsenic induces phosphorylation of histone H3 at serine 10 through Akt1, ERK2, and RSK2 but not MSK1. Inhibition of ERK2 by dominant-negative mutant ERK2 or the MEK inhibitor PD98059 causes inhibition of phosphorylation of histone H3 (serine 10). Deficiency of RSK2 also blocks the phosphorylation of histone H3 (serine 10) induced by arsenic but no inhibition of phosphorylation of histone H3 at serine 10 was detected in DN-MSK1 plasmid-transfected JB6 Cl 41 cells. In contrast, DN-MSK1 or the MSK1 inhibitor, H89, inhibits or totally blocks the phosphorylation of histone H3 at serine 28 by UVB.

Akt1 is a serine/threonine kinase that is activated by various stimuli, such as hormones, growth factors, and extracellular matrix components (30). Akt1 has been shown to promote cell survival by inhibiting apoptosis because of its ability to phosphorylate Bad, one of its primary targets (31). A number of studies have shown that Akt1 gene amplification and the Akt1 pathway may play a major role in stimulating proliferation and survival in cells overexpressing erbB2 in cancer (32). In this study, we report that Akt1 kinase is involved in arsenic-induced phosphorylation of histone H3 at serine 10 in JB6 cells. Both Akt1 kinase activity and phosphorylation of Akt1 at serine 473 increased when JB6 Cl 41 cells were stimulated with arsenic (Fig. 3). DN-Akt1 inhibited arsenic-induced phosphorylation of histone H3 at serine 10 and activated-Akt1 increased arsenic- induced phosphorylation of histone H3 at serine 10 compared with empty vector-transfected JB6 cells (Fig. 4). Moreover, using either pure histone H3 protein or chromatin, active Akt1 was shown to strongly phosphorylate histone H3 at serine 10 in vitro in a dose-dependent manner (Fig. 5).
These results indicated that Akt1 kinase plays a very important role in arsenite-induced phosphorylation of histone H3 at serine 10.

We reported that ERK2 and JNKs are involved in UVB-induced phosphorylation of histone H3 at serine 10. In the present research, ERK2 was also shown to mediate arsenite-induced phosphorylation of histone H3 at serine 10. DN-ERK2 and PD98059, a MEK inhibitor, almost totally blocked phosphorylation of histone H3 at serine 10 induced by arsenite (Fig. 6). But unlike UVB-induced phosphorylation of histone H3 at serine 10, JNKs had no effect on arsenite-induced phosphorylation of histone H3 at serine 10 (data not shown). These results indicated that ERK2 but not JNKs are involved in the mediation of arsenite-induced phosphorylation of histone H3 at serine 10.

MSK1 is involved in the phosphorylation of nucleosomal components (33) and UVB-induced phosphorylation of histone H3 at serine 28. An inactivation mutation in either the N- or C-terminal MSK1 kinase domain completely annuls its activity (33). We established stably expressed N- or C-terminal MSK1 kinase dead Jb6 C141 cells and found that either one inhibited UVB-induced phosphorylation of histone H3 at serine 28. In the present study, we confirmed our previous results (Fig. 7A) but found that the N- or C-terminal MSK1 kinase dead mutants had no effect on phosphorylation of histone 3 at serine 10 induced by arsenite (Fig. 7C and F). H89, a MSK1 inhibitor, suppressed 12-O-tetradecanoylphorbol-13-acetate- or epidermal growth factor-induced phosphorylation of histone H3 at serine 28 induced by UVB. However, in this study, H89 had no effect on phosphorylation of histone H3 at serine 10 induced by arsenite (Fig. 7I). So, these results indicate that MSK1 is not involved in the mediation of arsenite-induced phosphorylation of histone H3 at serine 10.

The formation of the MAPK-RSK pathway has been shown to be necessary for activation of the RSK isoform stimulated by growth factors in vivo (34). RSK2 has been implicated in the phosphorylation of histone H3 in response to mitogenic stimulation by epidermal growth factor (35). In this study, we found that arsenite-induced phosphorylation of histone H3 at serine 10 was almost totally blocked in a time- and dose-dependent manner by deficiency of RSK2, but deficiency of Rsk2 had no effect on total histone H3 or acetylation of histone H3 at lysine 9 (Fig. 8). These data strongly suggest that arsenite-induced phosphorylation of histone H3 at serine 10 is also mediated by RSK2.

In summary, this study shows that arsenite induces phosphorylation of histone H3 at serine 10, and Akt1, ERK2, and RSK2, but not MSK1, mediate arsenite-induced phosphorylation of histone H3 at serine 10. This pathway for arsenite-induced phosphorylation of histone H3 at serine 10 is distinctly different from the pathway of UVB-induced phosphorylation of histone H3 at serine 28 (Fig. 9). Akt1 is another kinase that mediates the phosphorylation of histone H3 at serine 10 in vitro and in vivo. The present study further provides powerful evidence illustrating the probable mechanisms of arsenite in carcinogenesis in cells or animal models. However, many questions, including how arsenite enters cells, still need to be answered.

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