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Arsenic-induced NFκB transactivation through Erks- and JNKs-dependent pathways in mouse epidermal JB6 cells

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Abstract

Tumor promoting effects of arsenic are believed to be associated with its transactivation activity on transcription factors, such as AP-1 and NFκB. However, the results from different groups studying the effects of arsenic on NFκB activation are contradictory in different cell models. Since arsenic is a strong skin carcinogen, we have investigated the activation of NFκB by arsenic in a mouse skin epidermal cell line, JB6 cells. Exposure of cells to arsenite or arsenate led to NFκB transactivation in mouse epidermal JB6 NFκB-luciferase reporter stable transfectants, C141 NFκB mass$_1$. This induction of NFκB activity by arsenic was dose- and time-dependent. The transactivation of NFκB by arsenic appeared to be through activation of Erks and JNKs pathways because increased NFκB activity by arsenic could be dramatically inhibited by either pre-treatment of cells with PD98059 or overexpression of dominant negative JNK$_1$. That Erks activation is required for arsenic-induced NFκB transactivation was further supported by the findings that arsenic-induced NFκB transactivation was impaired in JB6 30.7b cells, which were deficient in Erks. (Mol Cell Biochem **222**: 29–34, 2001)

Key words: arsenic, NFκB, MAP kinase

Abbreviations: NFκB – nuclear factor-κB; AP-1 – activator protein-1; Erks – extracellular signal-regulated protein kinases; MAPK – mitogen-activated protein kinase; P^+ – tumor promoter-sensitive; P^- – tumor promoter-resistant; JNKs – c-Jun N-terminal kinases; FBS – fetal bovine serum; MEM – minimal essential medium

Introduction

Arsenic is a well-recognized compound widely distributed in food, water, air and soil [1–3]. Arsenic exposure is accompanied by many diseases, such as cancers of the lung, skin and liver [2–6]. Arsenic is released to the atmosphere from both natural and anthropogenic sources. Global natural emissions of arsenic and arsenic compounds have been estimated to be 8000 tons each year, whereas anthropogenic emissions are about three times higher, 23,600 tons per year [7]. NIOSH estimated that 1.5 million industrial workers are potentially exposed to arsenic and its compounds during manufacturing and processing operations [8]. Arsenic can exist in many chemical forms. Inorganic trivalent arsenite and pentavalent arsenate are the most important forms in causing diseases [8, 9].

One of the sensitive targets for arsenic toxicity is the skin. Both inorganic and organic forms are absorbed by human and animal skin [8, 9]. Animal experiments show that following chronic exposure, arsenic accumulates in the skin and hair

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[8, 9]. Although arsenic is ingested and absorbed from the diet, the skin is a major target organ. Some previous studies suggested that the accumulation of arsenic in skin increased sensitivity of skin to ultraviolet (UV) light and elevated the risks of UV carcinogenic effects [10, 11]. Many cases of skin cancer have been recorded among peoples with occupational or medical exposure to arsenic [8, 9]. Epidemiological evidence has shown an excess of skin cancers following arsenic exposure. Although arsenic is acknowledged to be highly carcinogenic to human skin, its mechanism of action at the cellular and molecular level in skin is not well understood. Arsenite was demonstrated to promote altered gene expression and modify intra- or inter-cellular communications [12, 13]. Arsenite was found to be a potent stimulator of AP-1 activity, but not NFκB activity in Hela cells [14]. Ludwig *et al.* [15] reported that arsenite induces Erks activation through MAPK kinase 6/p38-dependent pathways. Recently, we demonstrated that low concentrations of arsenite induced Erks activation and this Erks activation was required for arsenite-induced cell transformation [13]. High concentrations of arsenic induced cell apoptosis through JNKs pathways [16]. Here we investigated the effects of arsenic on NFκB activation and the signal transduction pathways involved in NFκB activation.

Materials and methods

Cell culture and agents

Mouse epidermal JB6, C141 and 30.7b cells as well as their NFκB-luciferase reporter stable transfectants were cultured in monolayers in Eagle's minimal essential medium containing 5% fetal bovine serum (FBS), 2 mM L-glutamine, and 25 μg of gentamicin/ml [17]. Fetal bovine serum was from Life Technologies, Inc. (Rockville, MD, USA); Eagle's minimal essential medium (MEM) was from Calbiochem (San Diego, CA, USA); luciferase assay substrate was from Promega (Madison, WI, USA); both arsenite and arsenate were from Sigma (St. Louis, MO, USA).

Assay for NFκB activation in JB6 C141 cells

Confluent monolayers of JB6 C141 NFκB mass$_1$ cells were trypsinized, and 8×10^3 viable cells suspended in 100 μ l of 5% FBS MEM were added to each well of a 96-well plate. Plates were incubated at 37°C in a humidified atmosphere of 5% CO_2. Twelve to 24 h later, cells were starved by culturing them in 0.1% FBS MEM for 24 h. Then, the cells were exposed to arsenic (diluted in 0.1% FBS MEM at the concentration indicated; storage concentration of arsenic was 50 mM dissolved in PBS) for NFκB induction and maintained in culture. After various time periods, the cells were extracted with lysis buffer, and luciferase activity was measured using a luminometer (Monolight 2010). The results are expressed as relative NFκB activity or relative luciferase activity [18].

Statistical analysis

The significance of the difference in the NFκB activity was determined with the Student's *t*-test.

Results

Induction of NFκB in mouse epidermal JB6 cells by arsenite and arsenate

Arsenite and arsenate were reported to have no effect on NFκB activity in Hela cells [14]. To determine the effects of arsenic on NFκB activation in mouse epidermal cells, we incubated C141 NFκB mass$_1$ cells, a stable JB6 C141 transfectant with the NFκB-luciferase reporter, with either arsenite or arsenate. The results show that treatment of C141 cells with either arsenite or arsenate led to significant NFκB induction (Fig. 1). A dose-response study indicates a concentration dependent induction of NFκB activation by arsenic (Fig. 2a). A time-course study suggests that treatment of cells with arsenic resulted in maximal induction of NFκB activity (~ 70-fold) at 24–48 h of-arsenic treatment of cells (Fig. 2b). Then the NFκB activity returned to near basal levels (Fig. 2b). These results demonstrate that both arsenite and arsenate induce very strong activation of NFκB activity in mouse epidermal cells.

Inhibition of arsenic-induced NFκB activation by PD98059

Arsenic was reported to activate JNKs and P38 kinase as well as Erks in previous studies [13–15]. Our recent studies also demonstrate that arsenite could induce activation of Erks and JNKs in JB6 cells [13, 16]. To test the possible role of Erks activation in arsenic-induced NFκB activation in JB6 cells, we pretreated C141 NFκB mass$_1$ cells with PD98059, an MEK1-Erks pathway inhibitor, before exposure of cells to arsenic. The results show that pretreatment of cells with PD98059 results in marked inhibition of arsenic-induced NFκB activation (Fig. 3). These data suggest that Erks may play a role in arsenic-induced NFκB activation.

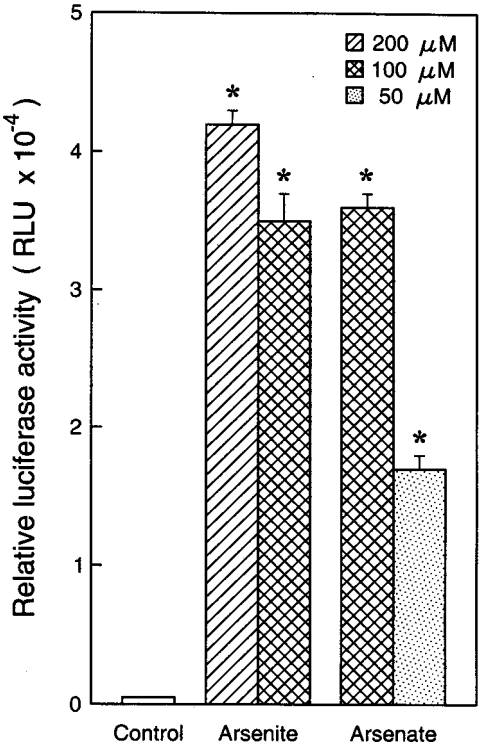

Fig. 1. Induction of NFκB activity by arsenic in mouse epidermal JB6 cells. 8×10^3 Cl41 NF B mass$_1$ cells were seeded into each well of 96-well plates. After being cultured at 37°C overnight, the cells were starved for 12 h by replacing medium with 0.1% FBS MEM. Then the cells were treated with either arsenite or arsenate at the concentrations indicated. After being cultured for 24 h, the luciferase activity was measured. The results are presented as relative luciferase activity. Each bar indicates the mean and standard deviation of 4 identically treated assay wells. *Indicates a significant increase from control ($p < 0.05$).

Arsenic-induced NFκB activation was impaired in JB6 30.7b cells

The JB6 mouse epidermal cell system includes tumor promotion-sensitive (P^+, C141) and tumor promotion-resistant (P^-, 30.7b) cells [18–22]. Our recent studies demonstrated that the lack of AP-1 activation and cell transformation responses to TPA and EGF in P^- cells is due to the shortage of Erks in this cell line. To further determine the role of Erks activation in arsenic-induced activation of NFκB, we compared NFκB activation of C141 NFκB mass$_4$ cells to 30.7b NFκB mass$_1$ cells. Results show that arsenic-induced NFκB activity was dramatically impaired in 30.7b NFκB mass$_1$ cells, while marked NFκB activation was observed in C141 NFκB mass$_4$ cells (Fig. 4). This result provides additional evidence that Erks activation is required for arsenic-induced NFκB activation.

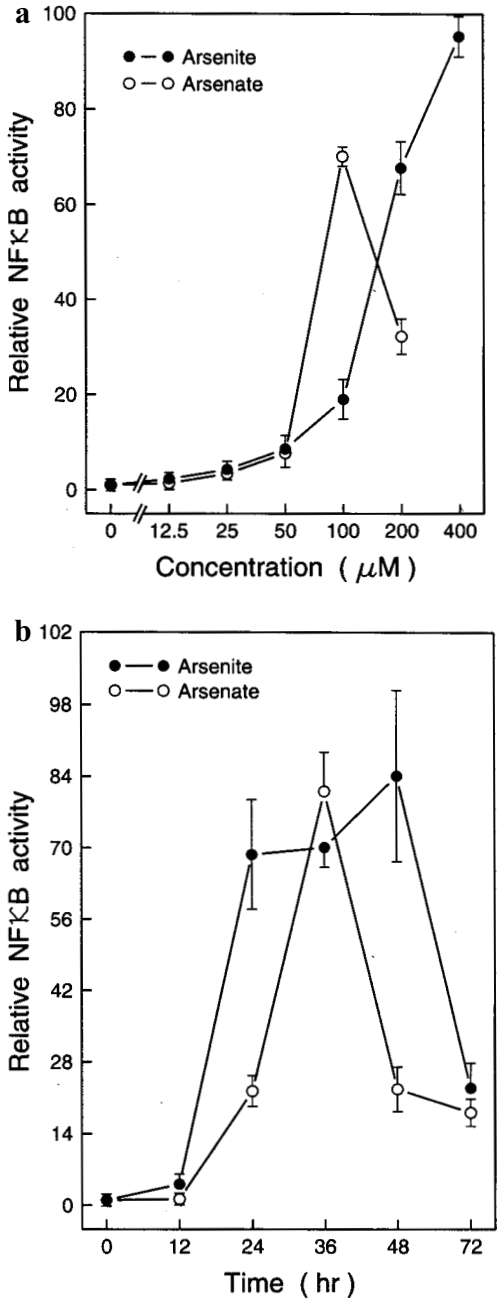

Fig. 2. Dose-response and time course-study of NFκB activation by arsenic. 8×10^3 C141 NFκB mass$_1$ cells were seeded into each well of 96-well plates. After being cultured at 37°C overnight, the cells were starved for 12 h by replacing medium with 0.1% FBS MEM. (A) For dose response study, the cells were treated with different concentrations of either arsenite or arsenate as indicated. After being cultured for 24 h, the luciferase activity was measured. The results are presented as relative NFκB activity. (B) For time course study, the cells were treated with either arsenite (100 μM) or arsenate (100 μM) for various times indicated and the luciferase activity was measured. The results are presented as relative NFκB activity. Each value indicates the mean and standard deviation of 4 identically treated assay wells.

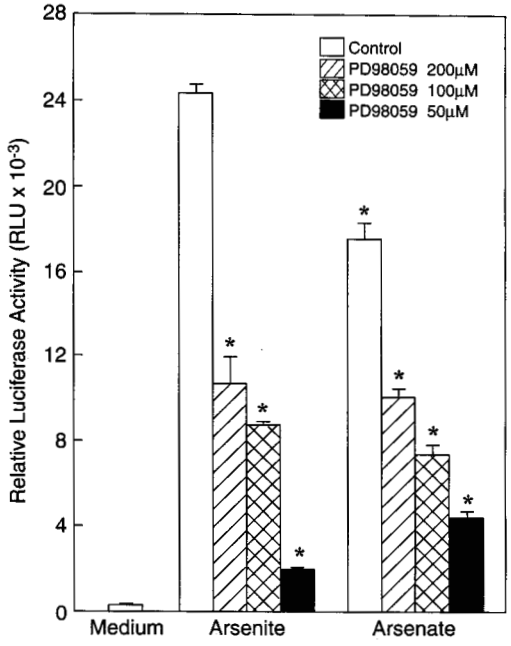

Fig. 3. Inhibition of arsenic-induced NFκB activity by pretreatment of cells with PD98059. 8×10^3 C141 NFκB $mass_1$ cells were seeded into each well of 96-well plates. After being cultured at 37°C overnight, the cells were starved for 12 h by replacing medium with 0.1% FBS MEM. Then the cells were first incubated with different concentrations of PD98059 for 30 min and then treated with either arsenite (100 μM) or arsenate (100 μM). After being cultured for 24 h, the luciferase activity was measured and the results are presented as relative luciferase activity. Each bar indicates the mean and standard deviation of 4 identically treated assay wells. *Indicates a significant increase from control ($p < 0.05$).

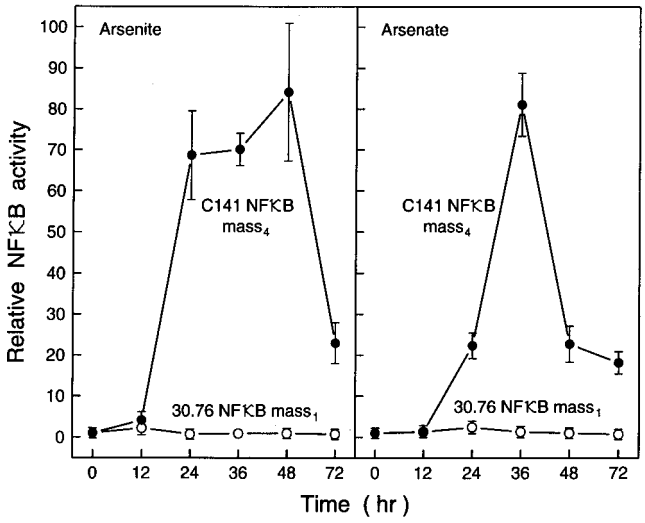

Fig. 4. Arsenic induces NFκB activation in JB6 C141 cells, but not in 30.7b cells. 8×10^3 C141 NFκB $mass_4$ cells or 30.7b NFκB $mass_1$ cells were seeded into each well of 96-well plates. After being cultured at 37°C overnight, the cells were starved for 12 h by replacing medium with 0.1% FBS MEM. Then the cells were treated with either arsenite (100 μM) or arsenate (100 μM) for various times indicated. The cells were harvested and the luciferase activity was measured. The results are presented as relative NFκB activity. Each value indicates the mean and standard deviation of 4 identically treated assay wells.

Blocking of arsenic-induced NFκB activation by overexpression of dominant negative JNK_1

Our previous results suggest that arsenite induces JNκB activation [13, 16]. To test possible involvement of JNKs in arsenic-induced NFκB activation, we used a well-characterized JB6 cell stable co-transfectants, C141 DN JNK_1 $mass_2$ and C141 DN JNK_1 $mass_4$ [13, 16, 23]. Results showed that arsenic-induced NFκB activity was dramatically blocked by overexpression of dominant negative mutant of JNK_1. This result demonstrates that JNK_1 was involved in the signal transduction pathway leading to NFκB activation in response to arsenic.

Discussion

In the present study, we investigated the effects of arsenite and arsenate on NFκB transactivation as well as its signal transduction pathways in mouse epidermal JB6 cell lines. The results show that treatment of NFκB-luciferase reporter transfected mouse epidermal C141 cells with either arsenite or arsenate leads to an increase in NFκB activity. This NFκB activation appears to be time- and dose-dependent. The induction of NFκB could be significantly inhibited by pretreatment of cells with PD98059, a specific inhibitor of MEK_1-Erks pathway. The important role of Erks in arsenic-induced NFκB activation was further supported by the finding that NFκB activation was impaired in 30.7b cell, a cell deficient in Erks, as compared with C141 cells that exhibit normal expression of Erks. Furthermore, the overexpression of the dominant negative mutant of JNK_1 also inhibited arsenic-induced NFκB activation. These results demonstrate that both arsenite and arsenate could induce NFκB transactivation in mouse epidermal cells, and that this induction appears to be mediated by activation of MAP kinase family members, including Erks and JNκB.

Environmental and occupational exposure to arsenic is associated with increased risk of skin, urinary bladder and respiratory tract cancers. A growing amount of evidence demonstrates that arsenic acts at the level of tumor promotion by activating the signal transduction pathways leading to activation of transcription factors, which in turn modulate the gene expression [12–15]. It has been reported that arsenite is a potent stimulator for induction of c-fos and c-jun gene expression, AP-1 transactivational activity and JNK activity, but not NFκB activity in Hela cells [14]. Ludwig *et al.* [15] reported that arsenite induces Erks activation through MAPK Kinase 6/p38-dependent pathways. Because the skin is one

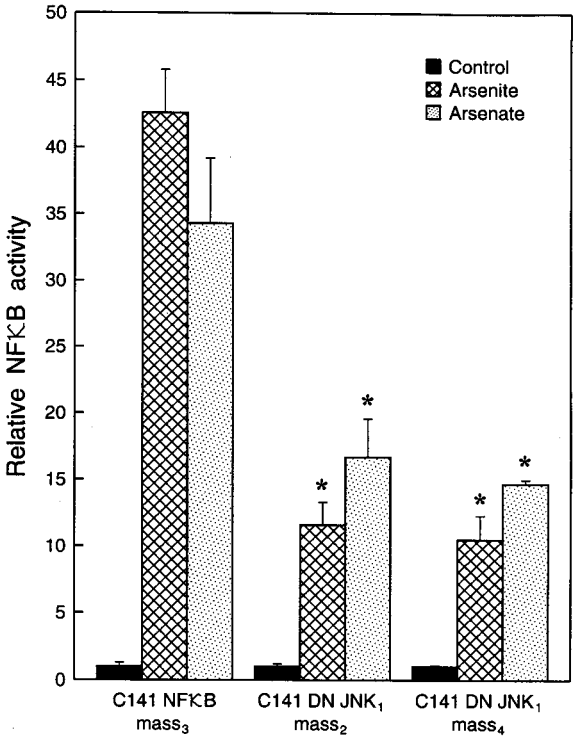

Fig. 5. Blockade of arsenic-induced NFκB activity by overexpression of dominant negative mutant JNK_1. 8×10^3 C141 NF B $mass_3$ cells, C141 DN JNK_1 $mass_2$ cells and C141 DN JNK_1 $mass_4$ cells were seeded into each well of 96-well plates. After being cultured at 37°C overnight, the cells were starved for 12 h by replacing medium with 0.1% FBS MEM. Then the cells were treated with either arsenite (100 μM) or arsenate (100 μM). After being cultured for 24 h, the cells were harvested and the luciferase activity was measured. The results are presented as relative NFκB activity. Each bar indicates the mean and standard deviation of 4 identically treated assay wells. *Indicates a significant increase from control ($p < 0.05$).

of the major targets of arsenic, we recently addressed the effects of arsenic on signal transduction pathways leading to activation of transcription factors and MAP kinases in mouse epidermal cell line, JB6 cells, and mouse skin [13, 24]. We demonstrate that low concentrations of arsenite induced Erks activation and that Erks activation was required for arsenite-induced cell transformation [13]. In contrast high concentrations of arsenite caused activation of JNKs, which mediated cell apoptosis in mouse epidermal JB6 cells [16]. Very recently, we also determined arsenic-induced activation of AP-1 *in vivo* using AP-1-luciferase reporter transgenic mice [24]. It was found that arsenic could induce activation of AP-1 *in vitro* and *in vivo* [24]. Arsenic was also found to induce activation of Erks, JNKs, and P38 kinase [13, 16, 24]. The induction of AP-1 activity by arsenic appears to be mediated by activation of PKC and MAP kinase family members, because induction of AP-1 could be dramatically blocked by either pretreatment of cells with PD98059 or overexpression of dominant negative mutant of PKC [24, 25]. The results from this study show that both arsenite and arsenate markedly induce activation of NFκB in mouse epidermal JB6 C141 cells, but not 30.7b cells, which had low levels of Erks [19], suggesting that Erks activation is involved in NFκB activation by arsenic. This notion was further supported by data that specific inhibition of arsenic-induced Erks activation by PD98059 dramatically inhibited NFκB activation induced by arsenic. Furthermore, it was also found that over-expression of dominant negative mutant JNK_1 also inhibited arsenic-induced NFκB activation, indicating that JNKs activation is also required for arsenic-induced NFκB activation. Because blockade of activation of either Erks or JNKs led to inhibition of arsenic-induced NFκB activation, we speculate that there may be cross-talk between Erks and JNKs in the JB6 cells response to arsenic stimulation, and that this cross-talk is required for NFκB activation.

NFκB has attracted widespread attention among researchers in many fields in the last decade [26, 27]. NFκB consists of two major subunits, p50 and p65 (Rel-A) [26, 27]. It exists in cells as an inactive cytoplasmic precursor by forming a complex with the IκB, an inhibitor for NFκB [26, 27]. Signaling leading to IκB phosphorylation triggers the release of NFκB from IκB, resulting in the activation and translocation of NFκB from the cytoplasm to nucleus where NFκB binds to the promoter region of its specific targeting genes [26, 27]. There is increasing evidence that activation of NFκB is a part of mechanisms involved in tumor promotion that has been demonstrated in different cell models by different groups [28–30]. NFκB was first considered to be a mediator of tumor promotion because of its ability to alter gene expression in response to tumor promoters and oncogenes, including bacterial lipopolysaccharide, TPA, TNF-α, UV radiation, metals, reactive oxygen species and Her2/Neu [18, 26, 30–32]. Two members of the NFκB family, v-rel and p52/lyt-10, and the IκB family member Bcl-3 are potentially oncogenic [26]. H-Ras and Raf-1 can also activate NFκB [33, 34]. Overexpression of the NFκB inhibitor, IκBa, blocked the ability of oncogenic Ras alleles to induce focus formation in 3T3 cells [35]. It was reported that v-Rel expressed in transgenic mice under T cell specific control caused early death of animals from multicentric aggressive T cell lymphomas, and that v-Rel was predominantly associated with p50 and partially with IκBα [30]. Further, it was found that crossing v-Rel transgenic mice with mice overexpressing IκBα caused a delay in death from leukemia [30]. In light of the important role of NFκB activation in tumor development, we investigated the signal transduction pathways leading to NFκB activation by arsenic in mouse the epidermal cell line, JB6 C141 cells. We found that both arsenite and arsenate induced activation of NFκB in JB6 cells, revealing that arsenic-induce NFκB activation may play a role in arsenic-NFκB induced carcinogenesis. In addition, results in this study show that arsenic-induced activation was inhibited by pre-treatment

of cells with PD98059 or overexpression of dominant negative mutant JNK_1, suggesting chemical agents or molecular approaches that target MAP kinase-NFκB pathways may block the carcinogenic effects of arsenic.

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