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ORIGINAL PAPER

Relationship between p38 signaling pathway and arsenic-induced apoptosis: a meta-analysis

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Abstract Arsenic exposure could induce apoptosis and cause related cancer. It was reported that p38 signaling pathway played a key transcriptional regulatory factor in arsenic-induced apoptosis. However, there were certain disputable questions about this point of opinion. Therefore, the relationship between p38 signaling pathway and arsenic-induced apoptosis was systematically reviewed and analyzed by meta-analysis. Twelve essays were analyzed with StataSE15.0 and Review Manager 5.3. The regulatory variables, such as normal cells and cancer cells, arsenic exposure time and exposure dose were analyzed by the subgroup analysis. The comprehensive effects were compared and analyzed by SMD method. Publication bias, the monolithic impact and heterogeneity were inspected. Subgroup analysis showed, when arsenic exposure was $\geq$ 5 μmol/l, the expression of Bcl-2 and Bax was down-regulated and the expression of p38 and Caspase-3 was up-regulated. When arsenic exposure was $<$ 5 μmol/l, the expression of Bcl-2, Bax, p38 and Caspase-3 was up-regulated. Arsenic exposure time ($\geq$ 48 h) or arsenic exposure dose ($\geq$ 5 μmol/l or $<$ 5 μmol/l) can promote the expression of p38. Arsenic exposure time was $\geq$ 48 h or exposure dose was $<$ 5 μmol/l in cancer cells, arsenic exposure dose was $\geq$ 5 μmol/l or exposure time was $<$ 48 h in normal cells, and they are statistically significant in the expression of p38. This study evaluates the role of p38 signaling pathway in arsenic-induced apoptosis, which is helpful to provide theoretical basis for the differentiation of arsenic-induced injury and the therapeutic mechanism of arsenic-induced apoptosis.

Keywords Arsenic · P38 · Induce · Apoptosis · Meta-analysis

Liping Wu and Xi Li contributed equally to this paper.

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Introduction

Arsenic is a natural and bioaccumulative toxic metal, which is often scattered among atmosphere, water, soil and organisms in the trivalent or pentavalent form (Organization W H 2004; Ahmed et al. 2015). Also, arsenic is a famous human cancerogenic substance, and the elementary contamination is harmful to human health (Benbrahim-Tallaa and Waalkes 2008;

Cheremisinoff 2016). Long-time arsenic exposure may produce dermis cancer, liver cancer, prostate cancer and other related diseases, and it is a public health problem of international concern (Kim et al. 2016).

Arsenic exposure can produce apoptosis. Apoptosis is an active and gene-directed form of death with obvious morphological and biochemical changes, involving caspase reaction energizing, DNA fracturing kernels, Omal fragments and the cleavage of various caspase substrates (Rojewski et al. 2004). The molecular mechanism of arsenic-induced apoptosis is unclear, and further research is needed (Ray et al. 2013; Eguchi et al. 2011). Relevant studies have shown that ROS played a key role in oxidative stress-induced apoptosis, propagation by activating MAPK can bring about necrosis and autophagy, and MAPK basically contains three mechanisms: ERK, p38 and JNK (Miao et al. 2013; Davison et al. 2004).

P38, normally renowned as stress activation protein kinases, is comprised of cell reproduction, apoptosis, phenotypic transformation and cell ischemia reperfusion injury (Dingar et al. 2010). P38 mitogen-activated protein kinase can respond to stress signals and inflammatory cytokines, mostly linked to apoptosis (Fan and Chambers 2001; Dent and Grant 2001). At all events, according to the interdependent literature, it is displayed that not all researchers agree with the problem of arsenic-mediated p38 signaling transduction. Some studies have shown that p38 signaling pathway promotes cell death (Sarkar et al. 2002) or cell survival (Liu et al. 2001), depending on cell type and kinase subtypes activated by various stress stimuli (Giafifis et al. 2006). We also observed that p38MAPK was activated at low concentrations and discrete time points of exposure to ATO that came with the manufacture of ROS, indicating that p38MAPK was also a downstream effect of ROS (Liu et al. 2010). Overtly, the effect of arsenic and its compounds on p38 signal pathway was always an unacceptable question.

This paper made a meta-analysis of the experimental studies published in the literature to evaluate the role of p38 signaling pathway in arsenic-induced apoptosis and explore the potential heterogeneity and potential effects between learnings. Simultaneously, it helped to provide a theoretical basis for the differentiation of arsenic-induced damage and the therapeutic mechanism of arsenic-induced apoptosis.

Materials and methods

Inclusion touchstones

The inclusion touchstones and literature retrieval terms were determined, based on the principles of Pico.

Research and design experimental studies were delivered in Chinese and English. Total cell ranges and animals were studied, despite body weight, age and gender.

We intervened all experimental groups treated with any kind of arsenic or its compound. Arsenic model group may show the change of p38 signal pathway and apoptosis-related indexes. If different exposure doses or exposure times of arsenic were used in the study, the highest or longest group was selected for analysis. The control group did not do any intervention in the control group (blank control).

Ending index: 1 = p38; 2 = P-p38; 3 = Akt; 4 = P-Akt; 5 = Bcl-2 (B cell Lymphoma/leukemia-2 protein); 6 = Caspase-3 (cysteine aspartate-specific protease-3); 7 = Cleaved caspase-3; 8 = Caspase-9; 9 = Cleaved caspase-9; 12 = FAS; 11 = Bax; 10 = Bcl-xl; 13 = XIAP; 14 = Survivin. Utterly confirmed studies were examined independently and carefully by two researchers to determine whether a study met the inclusion touchstones for the meta-analysis. If the two examiners cannot agree on the qualifications of an article, it would be arranged via another investigator.

Exclusion touchstones

We excluded these studies without results according to the criteria of: (1) Papers focusing on p38 and not studying arsenic. (2) Papers focusing on arsenic and not studying p38. (3) The following criteria exclude the absence of outcome indicators in these studies. (4) Repeated published. (5) Review articles. (6) Academic conference reports. (7) Did not have available experimental data.

Retrieval strategy

We used Web of Science, Wanfang dbase, Pubmed, CNKI, VIP dbase and EMBASE to search related articles published in English or Chinese and retrieved once for all in November 2019. We used the search

words "arsenic," "MAPK" and "p38." The key search string was "Arsenic and (MAPK or p38)." In addition, we referenced the retrieved articles reviewed to determine that our database searched for other uncaptured studies.

Quality evaluation

By Cochrane to appraise the bias risk, Cochrane was used to assess the quality of the 12 articles identified in this study. The assessment system constituted of seven situations as follows: (1) random sequence generation (selection bias), (2) allocation concealment (selection bias), (3) blinding of participants and personnel (performance bias), (4) blinding of outcome assessment (detection bias), (5) incomplete outcome data (attrition boas), (6) selective reporting (reporting bias) and (7) other bias.

Data collection

Two examiners (Liping Wu and Changyan Wu) independently extracted the data and then cross-checked the results before putting them into the collective spreadsheet. Provided the consequences seem to be skimble-scamble, it will be verified by Xi Li and Ting Hu before final confirmation.

The posterior messages: (1) information about the paper was carefully recorded from the complete manuscript of each qualified study, incorporating the headline, the initial writer, the date of publication and the name of the journal. (2) The feature of topics, including cell line type and source. (3) Arsenic type, exposure dose and time. (4) Result index. (5) Baseline data of the test group and the control group, videlicet: mean, standard difference (SD) and class number (N).

Data analysis

StataSE15.0 and Review Manager 5.3 were used to dissect 12 studies. The standard mean deviation (SMD) was selected to analyze the merging effect. The heterogeneity was detected by computing I^2 indicatrix. $I^2 \leq 50\%$ and $P > 50\%$ represent low and high levels of heterogeneity, in several. To utilize the random effect model, $P < 0.05$ and $I^2 > 50\%$. To utilize the fixed effect model, $P > 0.05$ and $I^2 \leq 50\%$. Subgroup analysis and meta-regression analysis (including univariate and multivariate regression analysis) were used to examine the sources of heterogeneity in 12 studies. The subgroup analysis was based on the source of arsenic (normal cells and cancer cells), arsenic exposure time ($\geq$ 48 h and $<$ 48 h) and arsenic exposure dose ($\geq$ 5 μmol/l and $<$ 5 μmol/l). The combined effect was estimated to be SMD with 95% confidence interval (95% CI) between the arsenic model and the control group. Overall, the recorded P importance was double-sided and statistically significant ($P < 0.05$). Funnel chart was used to estimate publication bias, and StataSE15.0 was presumed on sensitivity analysis.

Results

Elementary features of the choice research

Firstly, a total of 596 articles related to this research topic were searched from 6 databases, then 68 repeated articles were excluded from 596 articles, and 116 articles were obtained through topic screening and abstract screening. We eliminated the studies with synsemantic information; eventually, 12 essays were comprised, including 6 foreign studies (Chowdhuri et al. 2009, Alice et al. 2010, Namgung et al., Akanda et al. 2017, Qu et al. and Zhang et al. 2017) and 6 Chinese studies (Yang et al., Yuan et al., Su et al. 2013, Luo et al., Dong et al. and Chang et al.) (Fig. 1).

A total of 596 articles were initially identified by search criteria. According to our inclusion and exclusion touchstones, 12 essays were conformed to the meta-analysis (Fig. 1).

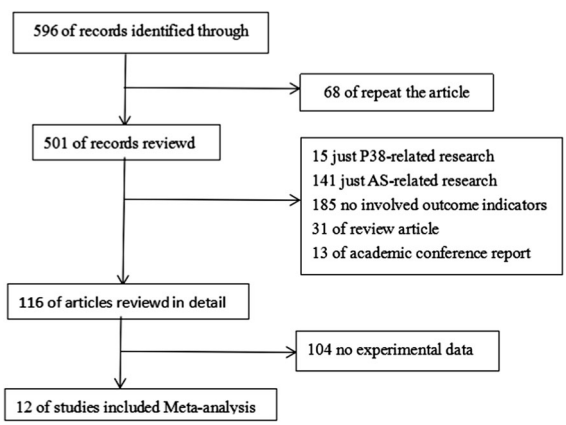

Fig. 1 Flowchart of identifying and including studies

Twelve studies were incorporated for this research, comprising natrium arsenite ($NaAsO_2$) and arsenic trioxide (As_2O_3). The control model was blank, and there was no arsenic exposure. The relevant data from the included studies showed that arsenic exposure time and arsenic exposure dose were concentrated at 48 h and 5 μmol/l, in several. The subgroup analysis was divided into ≥ 48 h (nasty 8) and < 48 h (nasty 4) according to the exposure time of arsenic, divided into ≥ 5 μmol/l (nasty 6) and < 5 μmol/l (nasty 6) according to arsenic exposure dose, and divided into normal cells (nasty 4) and cancer cells (nasty 8) according to different cell lines. In this review, cancer cells comprised the coming cells: Jurkat lymphoma cells, human lung carcinoma cell line (A549), HepG2 cells, prostate cancer cell line PC-3, human glioma cell line U87, human melanoma A375, human hepatoma cell line bel-7404 and K562 cell line. Normal cells comprised the coming cells: H9c2 rat ventricular, cerebellar granule neurons, the TRL 1215 cell line and encephalic cortical cells, to evaluate whether outcome variables (Cleaved caspase-3, Caspase-3, Apoptotic cells, Bax, FAS, Survivin, Caspase-9, Bcl-2, Cleaved caspase-9, XIAP, Bcl-xl) were linked with apoptosis and p38 signal pathway (Table 1).

Quality evaluation about the incorporated studies

We evaluated the quality methodology of the included studies (Fig. 2). There were 5 articles with low bias risk and high quality, 4 essays with access to 7 points and another 7 essays with medium bias risk. The standard was "+," the standard was "−," and the uncertainty was "?". It was a statistical chart showing the proportion of items in methodological evaluation (Fig. 3).

Meta-analysis conclusions

First of all, the overall effect test of all the selected samples showed that p38 signaling pathway played a crucial role in arsenic-induced apoptosis. The included studies were tested for overall homogeneity (I^2= 50%, $P < 0.05$), revealing that there was no heterogeneity in the middle of multiple researches. It was analyzed that there was heterogeneity among other groups of data in this meta-analysis. Accordingly, we used the fixed effect model, which reflected the possibility of potential regulatory variables. The results of double-tailed test ($P < 0.05$) showed that the combined statistics of multiple groups of data was statistically significant. The above data showed that p38 signaling pathway had a great effect on arsenic-induced apoptosis (Fig. 4, Table 2).

We carried out the meta-analysis of arsenic-related apoptosis based on the overall effects of apoptosis markers (Bax, P-Akt, Caspase-3 and Bcl-2). When $I^2 \leq 50$ (Bax, Bcl-2), the fixed effect model was used. When $I^2 \leq 50$ (Caspase-3, P-Akt), the random effect model was used. Experimental studies showed that arsenic exposure could down-regulate the expression of pro-apoptotic substances, such as P-Akt, and thus induced apoptosis; arsenic exposure could up-regulate the expression of pro-apoptotic substances, such as Bcl-2, Bax and p38, and therefore caused cell apoptosis. The related results were obtained by combining the apoptosis markers in the 12 articles included. To contradistinguish the control group, the expression of P-Akt and Bax was down-regulated in the arsenic exposure group, the expression of P-Akt in the arsenic exposure group (SMD = − 1.24, 95% CI [− 3.26 to 0.78]), and the expression of Bax in the arsenic exposure group (SMD = − 0.11, 95% CI [− 1.42 to 1.19]). To contradistinguish the control group, the expression of Bcl-2 and Caspase-3 was up-regulated in the arsenic exposure group, the expression of Bcl-2 in the arsenic exposure group (SMD = 0.80, 95% CI [− 1.76 to 3.37]), and the expression of Caspase-3 in the arsenic exposure group (SMD = 2.59, 95% CI [− 0.19 to 5.36]) (Fig. 5).

We carried out the subgroup analysis to determine the effect of arsenic on p38 according to exposure time. From the results, when arsenic exposure time was ≥ 48 h, the expression of p38 was up-regulated (SMD = 2.60, 95% CI [1.37–3.84], $Z = 4.41$, $P < 0.05$) (Fig. 6). But they are not statistically significant, when arsenic exposure time was < 48 h (Fig. 7). Therefore, this analysis showed that only arsenic exposure time with ≥ 48 h may up-regulate the expression of p38 and cause cell apoptosis.

We carried out the subgroup analysis based on arsenic exposure dose. The analysis showed that the expression of Bcl-2 and Bax was down-regulated in high dose of arsenic exposure (≥ 5 μmol/l) and the expression of Bcl-2 and Bax was up-regulated in low dose of arsenic exposure (< 5 μmol/l). The analysis showed that the expression of Caspase-3 was up-

Table 1 Elementary features of the choice research

References	Language	*n*	Type of arsenical compounds	Dose of arsenic, μmol/l	Time of exposure, h	Type of cells	Outcome indicators
Chowdhuri et al. (2009)	English	3	$NaAsO_2$	< 5	≥ 48	Cancer cells	1, 2, 3, 4
Alice et al. (2010)	English	5	As_2O_3	< 5	≥ 48	Cancer cells	1, 6
Namgung and Xia (2001)	English	3	$NaAsO_2$	≥ 5	≥ 48	Cancer cells	1
Akanda et al. (2017)	English	2	$NaAsO_2$	≥ 5	≥ 48	Cancer cells	2, 5, 6, 11
Qu (2002)	English	2	$NaAsO_2$	≥ 5	< 48	Normal cells	1, 5, 11, 12
Zhang et al. (2017)	English	4	As_2O_3	≥ 5	< 48	Normal cells	1, 2, 5, 6, 12
Yang and Zhenqiu (2012)	Chinese	3	As_2O_3	< 5	≥ 48	Cancer cells	1, 4, 6
Yuan et al. (2014)	Chinese	3	As_2O_3	< 5	≥ 48	Normal cells	1, 2
Su et al. (2013)	Chinese	3	As_2O_3	≥ 5	< 48	Cancer cells	1
Luo et al. (2011)	Chinese	2	$NaAsO_2$	< 5	≥ 48	Normal cells	1, 5, 11
Dong et al. (2017)	Chinese	3	As_2O_3	≥ 5	≥ 48	Cancer cells	2, 4, 6
Chang and Guangfu (2015)	Chinese	3	As_2O_3	< 5	< 48	Cancer cells	2, 5, 7, 9, 11, 13, 14

n: number of treatment groups; N: normal cells; C: cancer cells; p38; Akt: protein activase; Bcl-2: B cell lymphoma/leukemia-2 protein; Bax; Bcl-xl; Survivin; Caspase-3; 1 = p38; 2 = P-p38; 3 = Akt; 4 = P-Akt; 5 = Bcl-2 (B cell lymphoma/leukemia-2 protein); 6 = Caspase-3 (cysteine aspartate-specific protease-3); 7 = Cleaved caspase-3; 8 = Caspase-9; 9 = Cleaved caspase-9; 10 = Bcl-xl; 11 = Bax; 12 = FAS; 13 = XIAP; 14 = Survivin

regulated in low dose of arsenic exposure (< 5 μmol/l) and in high dose of arsenic exposure (< 5 μmol/l). However, the expression of p38 was up-regulated in high dose of arsenic exposure (≥ 5 μmol/l), p38 (SMD = 1.70, 95% CI [0.42–2.98], $Z = 2.59$, $P < 0.05$). The expression of p38 was up-regulated in low dose of arsenic exposure (< 5 μmol/l), p38 (SMD = 1.98, 95% CI [0.56–3.39], $Z = 2.73$, $P < 0.05$). This result clearly indicated that the expression of p38 was up-regulated by arsenic exposure in both high dose and low dose (Fig. 8a).

We carried out the subgroup analysis based on normal cells and cancer cells. The analysis showed that arsenic exposure could up-regulate the expression of Bcl-2 in normal cells or cancer cells. The analysis showed that arsenic exposure could up-regulate the expression of Bax in cancer cells and down-regulate the expression of Bax in normal cells. However, arsenic could up-regulate the expression of p38 in normal cells and cancer cells, and the bifurcation was statistically significant: in cancer cells, p38 (SMD = 2.05, 95% CI [0.80–3.29], $Z = 3.22$, $P < 0.05$) and in normal cells, p38 (SMD = 3.55, 95% CI [1.41–5.68], $Z = 3.26$, $P < 0.05$). This result clearly showed that arsenic exposure could increase the expression of p38 in both cancer cells and normal cells (Fig. 8b).

We carried out the subgroup analysis based on the effects of different exposure dose of arsenic and exposure time of arsenic on p38 in cancer cells and normal cells. In cancer cells, there is no statistical significance in the expression of p38, when arsenic exposure dose was ≥ 5 μmol/l and arsenic exposure time was < 48 h. In cancer cells, when arsenic exposure time was ≥ 48 h, p38 (SMD = 2.47, 95% CI [1.18–3.76], $Z = 3.75$, $P < 0.05$) (Fig. 9a), when arsenic exposure dose was < 5 μmol/l, p38 (SMD = 1.97, 95% CI [0.55–3.40], $Z = 2.71$, $P < 0.05$) (Fig. 9d). In normal cells, there is no statistical significance in the expression of p38, when arsenic exposure dose was < 5 μmol/l and arsenic exposure time was ≥ 48 h. In normal cells, when arsenic exposure dose was ≥ 5 μmol/l, p38 (SMD = 3.19, 95% CI [− 3.21 to 4.35], $Z = 2.78$, $P < 0.05$) (Fig. 9c), when arsenic exposure time was < 48 h, p38 (SMD = 2.80, 95% CI [0.20–5.41], $Z = 2.11$, $P < 0.05$) (Fig. 9b).

Since more than 10 essays were comprised in the meta-analysis, the bias test can be carried out (Xuyi and Jiqian 2002). The funnel chart of publication bias showed that the scatter points were distributed in the

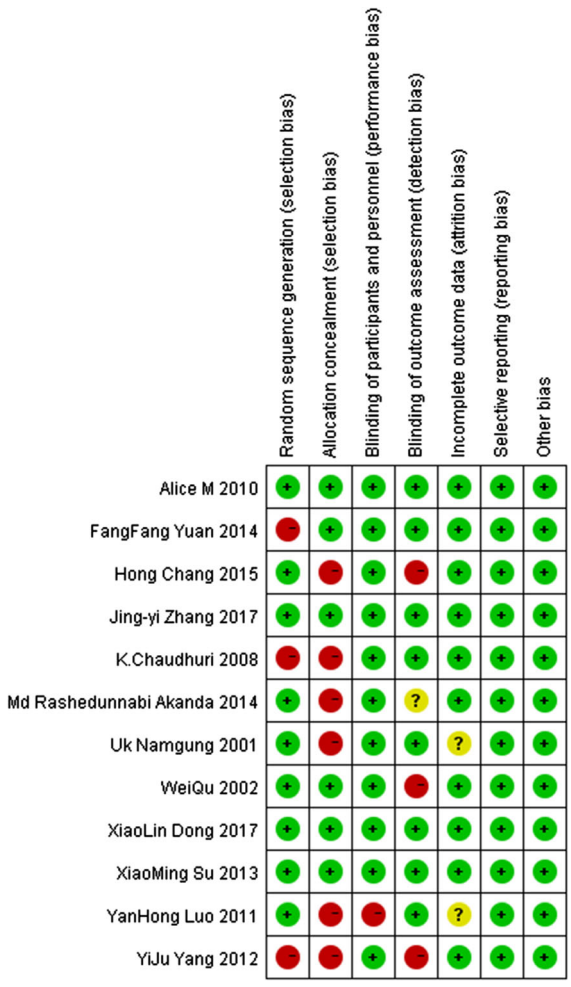

Fig. 2 Quality evaluation table

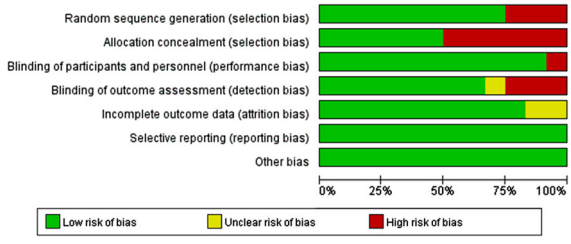

Fig. 3 Risk of deviation chart

upper position and were basically balanced between the left and right sides, but there was a slight bias in one article on the right, which will not have much impact on the results, indicating that the bias results were acceptable and there is no obvious publication bias among the studies (Fig. 10).

Sensitivity analysis showed that taking arsenic exposure and p38 signaling pathway as examples, the results included in the studies were uniformly distributed from the centerline with no significant deviation, and no separate result affects the overall results (Fig. 11). Therefore, the effect of the selected study was relatively stable.

Discussion

The quality evaluation and bias analysis of the 12 included articles were carried out in this meta-analysis. The events proved that they had senior firmness. It found that the combined effect of p38 signaling pathway on arsenic-induced apoptosis reached a large effect ($d = 2.31$), it is statistically significant, and p38 signaling pathway could boost arsenic-induced apoptosis. This study also included the literature on the quality of high and low bias risk, so these consequences were added and tried.

This paper was a meta-analysis study on the effect of p38 signaling pathway on arsenic-induced apoptosis based on animal experiments. Arsenic was destructive carcinogenic substance to people (IARC 2004). Long-term exposure to arsenic will bring serious harm to humans, animals and organisms (Rodríguez-Sosa et al. 2013). Numerous studies demonstrated that long-term arsenic exposure can cause apoptosis (Rojewski et al. 2004). Alice et al. (2010) found that arsenic trioxide can induce apoptosis in lung cancer (A549) cells and ATO can induce HepG2 cell apoptosis (Xinyang et al. 2020). It was previously reported that exposure to low concentrations of arsenic can lead to the death of head kidney macrophages (Soma et al. 2009). P38 has been reported to be involved in arsenic-induced apoptosis (Xiaowei and Yong 2003), and p38 inhibited arsenic-induced NF-κB activation (Jyotirmoy et al. 2009), but the report on the interaction between arsenic and p38 signaling pathway was inconsistent. Through the analysis, we found that p38 signaling pathway was expressed in both normal cells and cancer cells as long as arsenic exposure, which may be related to arsenic exposure dose and exposure time. These provided different theoretical basis for the discovery of arsenic-induced damage and effective treatment mechanism.

Different apoptosis markers played diverse roles in arsenic-induced apoptosis. From the analysis of the

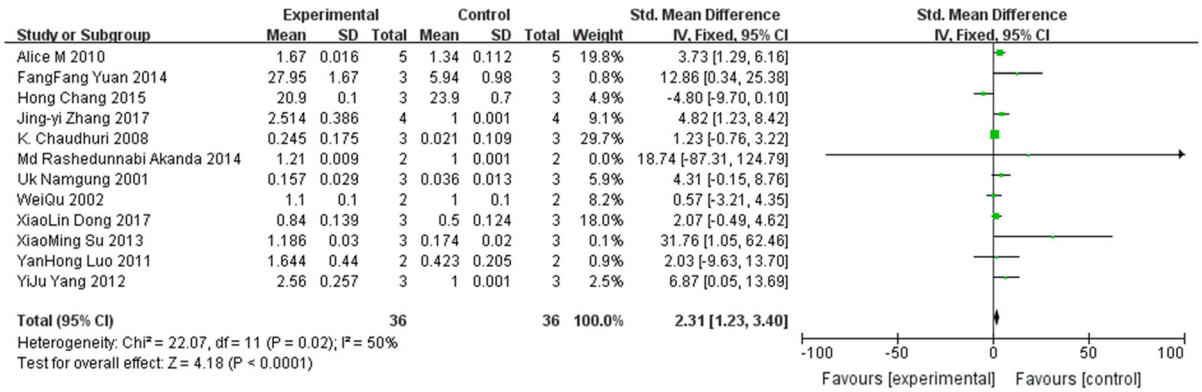

Fig. 4 Test diagram of overall effect. *SMD* standardized mean difference; 95% *CI* 95% confidence interval, *IV* independent variable

Table 2 Meta-analysis of the relationship between p38 signaling pathway and arsenic-induced apoptosis in this study

Fixed effect model	Independent sample	Homogeneity test			Bilateral test		Effect and 95% confidence interval
		x^2	P	I^2	Z	P	
	12	22.07	$P < 0.05$	50%	4.18	$P < 0.05$	2.31 (1.23, 3.40)

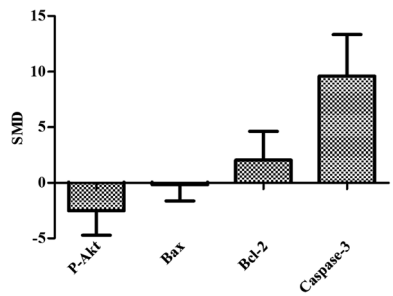

Fig. 5 Impact of arsenic on apoptosis markers. When the SD value was all bigger than the mean value, the extracted data had a higher degree of discretization. *SMD* standard mean difference; Caspase-3; Bax; Akt; Bcl-2

results, there was no statistical significance about P-Akt, Bcl-2, Bax and Caspase-3 (Fig. 5) and this may be due to the limited number of documents included. But the statistical significance did not represent their practical significance, because there were a large number of studies that were inconsistent with the results of this study. The representative of p38 protein growth boosts apoptosis, considering that P-Akt was down-regulated, and Caspase-3-mediated PARP cleavage has been displayed to induce apoptosis in all kinds of malignant cell lines, including human glioma cells and CaCO-2 colon cancer cells (Yang and

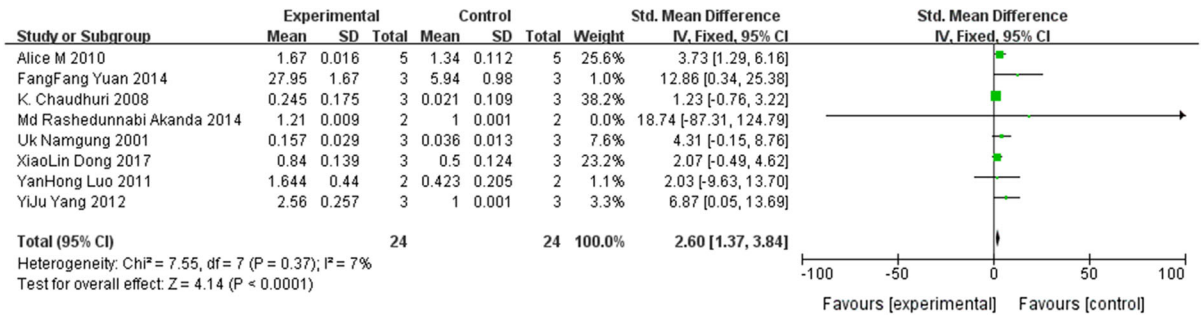

Fig. 6 Subgroup analysis to determine the effect of arsenic on p38 according to exposure time (≥ 48 h). The summary column represents the total number of studies performed that have been redefined. *SMD* standardized mean difference, 95% *CI* 95% confidence interval, *IV* independent variable

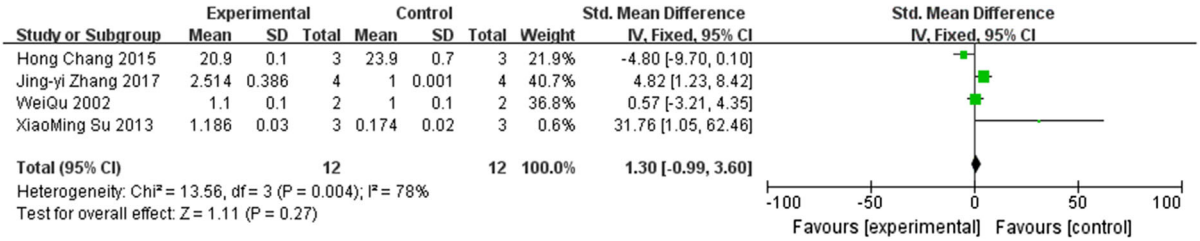

Fig. 7 Subgroup analysis to determine the effect of arsenic on p38 according to exposure time (< 48 h). The summary column represents the total number of studies performed that have been redefined. *SMD* standardized mean difference, 95% *CI* 95% confidence interval, *IV* independent variable

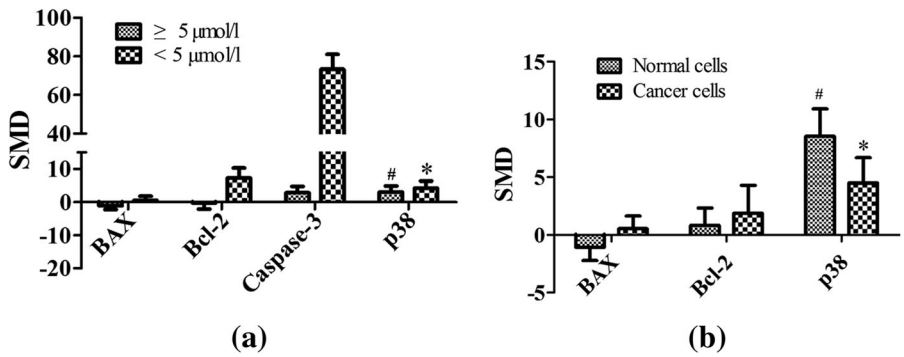

Fig. 8 **a** Effects of arsenic on apoptotic markers in arsenic exposure dose. **b** Effects of arsenic on apoptotic markers in cancer cells and normal cells. When the SD value was all higher than the mean value, the extracted data had a higher degree of discretization. *SMD* standard mean difference; Akt; Bax; Bcl-2; Caspase-3; $^{\#}P < 0.05$; $^{*}P < 0.05$

Zhenqiu 2016; Wenbin et al. 2014; Ruemmele et al. 1999). Zhang et al. (2017) found that it decreased the expression of Caspase-3 protein and the ratio of Bcl-2/Bax, at least partially inhibited ATO-induced apoptosis by regulating MAPK signal pathway. It is possible that due to the insufficient number of included articles, this data merge analysis cannot fully show the role of each apoptosis marker. Therefore, the down-regulated expression of Caspase-3 protein activity, anti-apoptotic protein (Akt, Bcl-2) and pro-apoptotic protein (Bax) (Das et al. 2010) is the conclusive evidence of arsenic-induced apoptosis.

The current results showed that p38 signaling pathway played the same role in normal cells and cancer cells. Alice et al. (2010) and Su et al. (2013) reported that arsenic-induced apoptosis was achieved by activating p38 signaling pathway in normal cells. Arsenic can increase the expression of p38 in normal cells, indicating that arsenic exposure can lead to the activation of p38 signaling pathway (Fig. 8b). It reported that arsenic-induced apoptosis of cancer cells was related to p38 (Chowdhury et al. 2009). ATO-induced apoptosis in human cervical cancer cells was due to the activation of p38 signaling pathway (Yan et al. 2018). Equally, the representatives of Bcl-2 and Bax were reduced in cancer cells (Fig. 8b), while the expression of Caspase-3 and p38 was increased. Arsenic expose could cause p38 signaling pathway, arsenic may cause toxicity by activating p38 signaling pathway in normal cells, and arsenic may promote tumor development by activating p38 signaling transduction. Obviously, the element of arsenic-induced apoptosis was the same in normal cells and cancer cells.

The difference of arsenic exposure dose and exposure time may affect the activity of p38. The results showed that the up-regulated expression of p38 promoted apoptosis when arsenic exposure time was ≥ 48 h (Fig. 6), and when arsenic exposure dose was ≥ 5 μmol/l, the representatives of p38 will be up-regulated and boosted the apoptosis (Fig. 8a). Namgung and Xia (2001) found that increasing the concentration and time of arsenite can activate p38 signaling pathway, because 10 μmol/l sodium arsenite

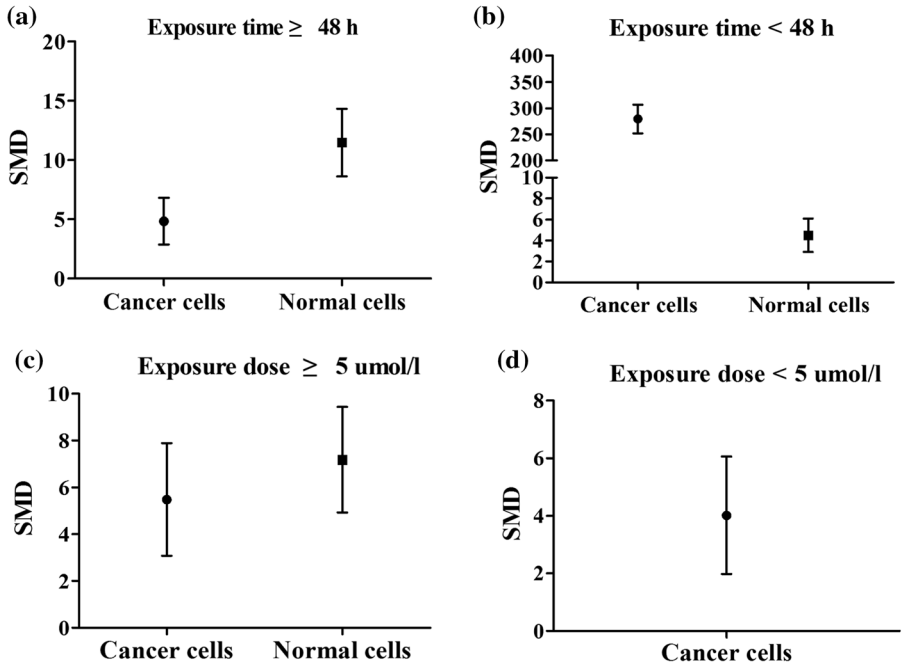

Fig. 9 Subgroup analysis based on the effects of different exposure doses of arsenic and exposure time of arsenic on p38 in cancer cells and normal cells. **a** Arsenic exposure time was ≥ 48 h; **b** arsenic exposure time was < 48 h; **c** arsenic exposure dose was ≥ 5 μmol/l; and **d** arsenic exposure dose was < 5 μmol/l. *SMD* standardized mean difference, *95% CI* 95% confidence interval, *IV* independent variable

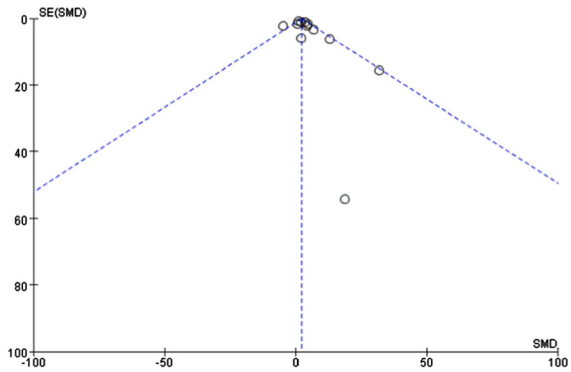

Fig. 10 A funnel diagram of p38. *SMD* standard mean difference, *SE* standard error

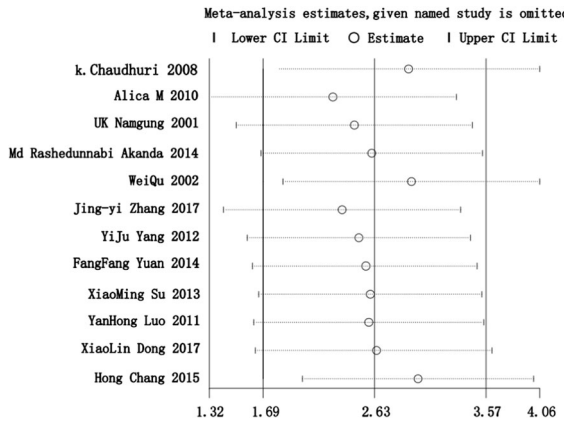

Fig. 11 Susceptivity analysis of p38

has a stronger inducing effect on apoptosis than 5 μmol/l sodium arsenite, which has also been confirmed by other studies (Zhang et al. 2017; Yang and Zhenqiu 2012). However, certain investigators (Chang and Guangfu 2015) have shown that low dose arsenic exposure may inhibit p38 signaling pathway. These occurrences were concordant with the consequence of meta-analysis, indicating that high dose of arsenic and long exposure time of arsenic may lead to the activation of p38 signaling pathway, while low dose of arsenic and short exposure time of arsenic may inhibit the activation of p38 signaling pathway. As_2O_3 has strong anti-tumor effect in vivo and in vitro, its effect depends on the dose. Low concentration of As_2O_3 ($\leq$ 0.5 μmol/l) induces differentiation, while high concentration of As_2O_3 ($>$ 2 μmol/l) induces apoptosis (Yuan et al. 2014; Tallman 2001). It was

worth noting that in the subgroup analysis of arsenic exposure time, the participant information was selected from the 12 items contained. Although the effect of p38 expression was the highest in more than 48 h, only 3 articles were comprised in more than 48 h. Most of the articles were concentrated between 24 h and 48 h. Therefore, there may be some deviation in the conclusions drawn from a few studies, and more studies need to be included in the future to explore the two regulatory variables of exposure dose and exposure time.

Conclusion

Going through the argumentation, it was concluded that arsenic was exposed for a long time in normal cells and p38 signaling pathway may be motivated and brought apoptosis. For cancer cells, arsenic exposure may activate p38 signaling pathway and promote apoptosis, restraining phyma progress. The longer the arsenic exposure time and the higher the arsenic exposure dose, the more conducive to the up-regulation of p38; this ending can give rise to apoptosis. These findings not only provided an effective way for p38 inhibitors of arsenic poisoning, but also provided a theoretical basis for long-term treatment of cancer with low dose arsenic.

Limitations and viewpoints

This learning may be blocked by else unmanageable elements. First of all, copyright and other causes of retrieval cannot be part of the study, resulting in the inclusion of the study that was not comprehensive, because the results of the analysis can also be explored on a larger scale. Then, seeing the publication bias was occurred, which was unbearable to operate all involved studies, and the omission of key adverse outcomes will result in false positive results. The 12 animal treatment groups were comprised, seeing the datum was no explicit, and it was not known whether the researchers in the original paper used the equivalent method to achieve the unpredictability of the random sequence, causing allocation concealment to be deficient, leading to a high risk of this study. It may be selected by opening randomized tables, using envelopes without proper security, alternately or cyclically, and seeding the animal number. In addition, the quality evaluation and complex data integration of the study may affect the heterogeneity to some extent. Ultimately, seeing the boundaries of literature data, this meta-analysis only analyzed normal cells and cancer cells, arsenic exposure time and exposure dose, exposure dose and exposure time of arsenic on p38 in cancer cells and normal cells, and more regulatory variables need to be explored in the future. Although this study revealed the regulatory effect of arsenic on p38 signaling pathway, the farther experimental investigation was devoid yet, and the specific molecular mechanisms did not seem to be sufficient, such as the effects of P-Akt and Bcl-2 on p38 signaling pathway. Therefore, it will play a vital tendency of ulterior investigation.

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Compliance with ethical standard

Conflict of interest The authors declare that they have no competing interests.

Availability of data and material Our data are from the website, so in our study we used collected data for the research.

Ethics approval and consent to participate This article does not contain any studies with human or animal subjects performed by any of the authors. All participants gave informed consent before taking part in the study.

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