INPLASY PROTOCOL

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None.

PTEN regulates arsenic-inducedn autophagy in PI3K/AKT/mTOR signaling pathway; A systematic review and meta-analysis of in vivo and in vitro studies

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Review question / Objective: **Is PTEN involved in arsenic-induced autophagy through the PI3K-AKT-mTOR signaling pathway in vivo and vitro studies?**
Condition being studied: **PTEN and arsenic-induced autophagy.**
Information sources: **We will retrieve Cochrane Library, PubMed , EMBASE , Web of Science , Allied and Complementary Medicine Database, VIP database, and China National Knowledge Infrastructure from inceptions to the present. All electronic database sources will be searched from inception to the present without limitations of language and publication status. The search strategy for Cochrane Library is created. We will also adapt similar search strategies and will apply them to the other electronic databases. We will include all eligible case-controlled studies that report associations between PTEN and arsenic-induced autophagy in vivo and vitro studies. In addition, we will also examine other literature sources, including conference proceedings and reference lists of related reviews.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 4 January 2021 and was last updated on 4 January 2021 (registration number INPLASY202110012).

INTRODUCTION

Review question / Objective: **Is PTEN involved in arsenic-induced autophagy through the PI3K-AKT-mTOR signaling pathway in vivo and vitro studies?**

Condition being studied: **PTEN and arsenic-induced autophagy.**

METHODS

Search strategy: **The search was conducted in Cochrane, Pubmed, Web of Science, Embase, China National Knowledge Infrastructure (CNKI) and Wanfang database. The deadline was taken as January 15, 2020. Keywords included: arsenic, arsenite, autophagy,PTEN, PI3K,**

PIK3CA, AKT, mTOR, LC3, Beclin1, VMP1, ATG5-12, ATG4 The specific strategy implied was: ((arsenic) OR (arsenite) OR (ATO) OR (AS2O3)) AND ((PI3K) OR (PIK3CA))AND ((PDK) OR (AKT)OR(p-AKT))AND (PTEN) AND (LC3) AND((mTOR) OR (mTORC1)OR(p-mTOR))AND ((ATGS) OR(ATG5) OR (ATG6) OR (ATG7) OR (ATG8) OR (ATG9) OR(ATG10)OR (ATG11) OR (ATG12))AND (SQSTM-1/P62) OR(autophagy).

Participant or population: Inclusion criteria: (1) All studies determined according to PICO principles . Participants (P): Cells, animals or people; Intervention (I): The experimental group treated with arsenic or arsenic compounds, the highest dose or longest duration of arsenic was used in the study; Comparison (C): The control group was a blank control group without any intervention; Outcome (O): FKBP-rapamycin-associated protein (mTOR) p-mTOR, , PI3K(PIK3CA), AKT,p-AKT, PTEN and autophagy indicators (LC3 , Beclin-1 ,ATG4-12,SQSTM-1/P62). (2) Type of research: Experimental research published either in Chinese or English. Exclusion criteria: (1) Not a Chinese or English literature, title is not relevant, abstract does not contain arsenic and PI3K/AKT/mTOR or autophagy. (2) Repeated articles (the same article is published in both Chinese and English magazines). (3) The data information in the article is incomplete and cannot be extracted. (4) The experimental group is not simply using arsenic intervention. (5) Non-experimental research.

Intervention: Experimental group: Detect the role of PTEN in PI3K/AKT/mTOR pathway which arsenic-mediated autophagy in cells, animals, and humans.

Comparator: Normal cells, animals, and human.

Study designs to be included: All case controlled studies on exploring the associations between PTEN in PI3K/AKT/mTOR pathway and arsenic-mediated autophagy will be included.

Eligibility criteria: All potential PTEN exploring the association between arsenic and PI3K/AKT/mTOR pathway will be considered.

Information sources: We will retrieve Cochrane Library, PubMed , EMBASE , Web of Science , Allied and Complementary Medicine Database, VIP database, and China National Knowledge Infrastructure from inceptions to the present. All electronic database sources will be searched from inception to the present without limitations of language and publication status. The search strategy for Cochrane Library is created. We will also adapt similar search strategies and will apply them to the other electronic databases. We will include all eligible case-controlled studies that report associations between PTEN and arsenic-induced autophagy in vivo and vitro studies. In addition, we will also examine other literature sources, including conference proceedings and reference lists of related reviews.

Main outcome(s): We will assess the outcome indicators based on the studies concerning the association between PTEN and arsenic-mediated autophagy, such as gene and protein expression of PTEN, outcome variables were FKBP-rapamycin-associated protein (mTOR) p-mTOR, , PI3K(PIK3CA), AKT,p-AKT, and autophagy indicators(LC3 ,Beclin-1 ,ATG4-12,SQSTM-1/P62).

Data management: Two researchers will independently collect data using standard data extraction form. The following information consists of basic information (study ID, publication time and source, first author, etc), characteristics of study (study setting, study methods, sample size, etc), intervention and control indexes, outcomes, results and findings. Any disagreement will be solved by discussion with another researcher.

Quality assessment / Risk of bias analysis: The quality of eligible studies will be assessed by two researchers using The Newcastle-Ottawa Scale. Any division will

be solved by another researcher through consultation, and a consensus will be reached.

Strategy of data synthesis: The mean ± standard deviation was used to describe the expression of each index in the experimental and control groups. The standardized mean difference (SMD) was used to compare and analyze the numerical data with different units or mean difference. The calculation formula of SMD is used to reflect the heterogeneity of the included literature, according to the Cochrane Handbook . Heterogeneity is divided into three categories: 0% to 25%, indicating mild heterogeneity; 25% to 50% signifying moderate heterogeneity; 50% to 75% with high heterogeneity. The random effect model was used when P < 0.05 and I2 > 50%. The fixed effect model was employed when P > 0.05 and I2 ≤ 50%. Further, a subgroup analysis was utilized to investigate the source of heterogeneity. The meta subgroup analysis was based on treatment time (< 24 h vs. 24-48 vs.≥48 h), arsenic concentration (≤5 μmol/L vs. > 5 μmol/L), cell type (normal vs. cancer cells), mice species (mice vs. rat vs. guinea pigs vs.chickens), intervention (drinking vs. gavage), and arsenic species (NaAsO2 vs. AS2O3 vs. DMA) in determining the relationship between grouping factors and outcome measures. The results of the combination of the experimental and the control group were expressed by SMD and 95% confidence interval (95% CI). Bilateral tests were used for statistical analysis of all indicators and when P ≤ 0.05 was considered statistically significant.Data analysis was performed using Review Manager Version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration 2012, and Stata 12.0 (Stata Corp LP, College Station, TX, USA) software. Graphpad Prism 6 software is also used to make images. The funnel plot was applied to reflect literature publication bias, and the hypothesis test used chi-square values. When P < 0.05, we considered it a publication bias. Stabilities of synthetic results were evaluated with sensitivity.

Subgroup analysis: Subgroup analysis and meta-regression test will be conducted according to the characteristics of the study participants, study quality, and sample size.

Sensibility analysis: We will use sensitivity analysis to test the stability and reliability of meta-analysis. It will be conducted by 2methods: eliminating each study one by one; using random-effect model (DerSimonian & Laird method) to test the results after using the fixed effect mode.

Language: English and Chinese literature.

Country(ies) involved: China.

Keywords: PTEN; arsenic; autophagy; PI3K/AKT/mTOR pathway.

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