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Association between klotho expression and malignancies risk and progression: A meta-analysis

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ABSTRACT

Background: We assessed the association between tissue klotho protein expression and the risk and progression of malignancies.

Methods: We searched the electronic databases for the studies regarding the relationship between tissue klotho protein expression and risk/progression of malignancies through January 2018. We calculated the pooled odds ratios (ORs) and corresponding 95% confidence intervals (CIs) to evaluate the impact of tissue klotho protein expression on malignancies. A fixed-effect model, or in the presence of heterogeneity, random- effect model was applied to calculate the combined ORs.

Results: Eighteen studies were recruited in our pooled-analysis. Overall malignancies including liver cancer, pancreatic ductal adenocarcinoma (PDAC), ovarian cancer, esophageal squamous cell carcinoma (ESCC), neuroendocrine cancer, oral cancer and bladder cancer demonstrated significantly lower ORs than those in controls ($p < 0.05$). Malignancies with tissue klotho protein expression showed a pooled hazard ratio (95% CI 0.784–2.479). Malignancies with tissue klotho protein expression showed a similar OR (95% CI 0.732–1.335) of male/total to cases without tissue klotho protein expression. Malignancies with tissue klotho protein expression showed a markedly lower OR (95% CI 0.454–0.941) of metastasis compared with those without tissue klotho protein expression. Malignancies with tissue klotho protein expression showed a markedly higher OR (95% CI 1.041–1.800) of stage I-II/III-IVcompared with those without tissue klotho protein expression. Malignancies with tissue klotho protein expression showed a similar OR (95% CI 0.948–3.407) of differentiation to cases without tissue klotho protein expression. Sensitivity analysis did not change the overall results significantly. No marked publication bias was noted.

Conclusions: Tissue klotho protein expression was associated with a lower risk and progression of malignancies. Klotho may be a protective factor against malignancies risk/progression.

1. Introduction

Klotho, an anti-aging gene, composed of five exons and four introns, is located in chromosome 13q12 [1]. Klotho exerts effects mainly in extending life span. Klotho deficiency mice demonstrated aging-like phenotypes and shortened life span [2]. Besides the anti-aging property, klotho also plays an important role in maintaining the cellular homeostasis [3]. Evidence showed that klotho protected against inflammation, oxidative stress and endothelial injury [4–6]. Klotho has been proved to be a therapeutic target of various diseases, such as chronic kidney diseases and atherosclerosis [7,8]. The multiple properties of klotho attract the attention of researchers and doctors.

Dysregulation of klotho was noted in several malignancies and was associated with the proliferation and apoptosis of tumor cells [9]. Klotho was involved in the pathogenesis of several tumors and regarded as an antitumor molecule. By contrast, klotho also stimulated angiogenesis and inhibited apoptosis [10], which may promote the growth of tumor. Currently, a number of studies have been performed to investigate the association between klotho and various malignancies [11–28]. However, the impact of klotho on malignancies risk and progression have not been fully elucidated. A comprehensive understanding of this issue may have important clinical implications given the possibility that klotho may be involved in the pathogenesis of malignancies and klotho may be a potential therapeutic target. A previous review [29] showed that the downregulation of klotho led to the increased proliferation and reduced apoptosis of cancer cells. However, the pooled quantitative analysis regarding the association between klotho and malignancies risk and progression was rare, which can yield a more convinced outcome. Meta-analysis is a good way to pool the existing evidence to provide a robust quantitative result.

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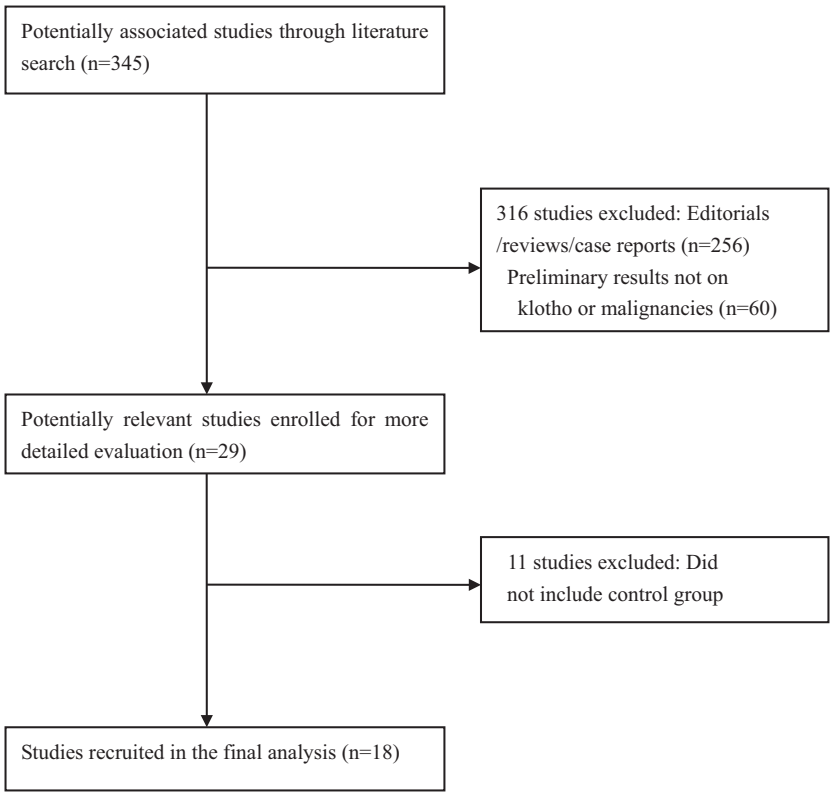

Fig. 1. Flow chart of study selection.

With the accumulating evidence, we, therefore, performed this meta-analysis to investigate the association between tissue klotho protein expression and malignancies risk/progression with the aim of providing a much more reliable finding on the significance of the association.

2. Methods

2.1. Search strategy

We searched the published papers that reported the tissue klotho protein expression through January 2018 by using PubMed, Embase and Cochrane databases. No restriction was imposed on search language. The used search terms were as follows: (1) klotho; and (2) malignancy, carcinoma, cancer. We searched the related publications by combining the term (klotho) and term (malignancy, cancer or carcinoma). We also reviewed the reference lists of extracted reviews and articles. If the same participants were enrolled in more than one study, we chose the study with the most complete analysis.

2.2. Inclusion and exclusion criteria

Inclusion criteria: (1) cohort, case-control or observational study; and (2) tissue klotho.

expression as one of the outcome interests; and (3) malignancies as cases; and (4) hazard ratio(HR)/relative risk(RR)/odds ratio(OR) with 95% confidence intervals (CIs) available (data to calculate them). Exclusion criteria: (1) case reports, editorials and reviews; (2) association between other factors and malignancy; and (3) multiple publications of the same data.

2.3. Data extraction and synthesis

We extracted study characteristics from each study. Data were recorded as follows: first author's surname, year of publication, ethnicity, study design, number of malignancies and controls, HR, male/female, differentiation, metastasis and stage. Two authors independently conducted the data extraction with any disagreements resolved by discussion.

2.4. Statistical analysis

Odds ratios werer used to measure the association between tissue klotho protein expression and malignancies risk/progression across studies. Heterogeneity of ORs among studies was tested by using the Q statistic (significance level at $p < 0.10$). The I^2 statistic,

a quantitative measure of inconsistency across studies, was also calculated. The combined ORs were calculated using a fixed-effect model, or in the presence of heterogeneity, a random-effect model. In addition, 95% confidence intervals (CIs) were also calculated. Subgroup analyses were conducted according to the type of malignancy. Potential publication bias was assessed by Egger's test and Begg rank correlation test at the $p < 0.05$ level of significance when the number of enrolled studies was > 10. Sensitivity analysis was conducted by omitting every study in each turn. All analyses were performed using STATA ver 12.0. A $P < 0.05$ was considered statistically significant, except where otherwise specified.

3. Results

3.1. Literature search

We initially extracted 345 relevant publications from the PubMed, Embase, Cochrane and China National WanFang databases. Of these, 327 studies were excluded according to the inclusion and exclusion criteria, 18 articles [11–28] were included in our meta-analysis (Fig. 1). The retrieved data were recorded as follows: first author's surname, publication year, ethnicity, study design, gender, the number of