

A Meta-Analysis of the Association Between SIRT1 Expression with Tumors Drug-Resistance

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Abstract: Objective: SIRT1(silent information regulator 1), a member of the highly conserved sirtuins family, has been reported to be abnormally expressed in a wide variety of cancers. Numerous studies have reported the association between SIRT1 and cancer drug resistance, but the data of different reports remains controversial. To further evaluate the role of SIRT1 in tumor resistance, a meta-analysis based on published studies was conducted. Methods: Relevant articles before September 2018 on SIRT1 and Drug-resistant tumor were searched via PubMed, Embase, Web Of Science (WOS). The studies were chosen for the meta-analysis based on requisite criteria. The relation was analyzed using RevMan 5.3 software. Odds ratios (OR) and their 95% corresponding confidence intervals (CI) were pooled to estimate the effect of specific associations. Results: A total of 14 eligible studies containing 790 patients were included, in which most of the patients overexpressed SIRT1. The results showed that SIRT1 overexpression significantly correlated with the risk of cancer drug resistance (OR=7.99, 95% CI: 5.70–11.21, $P<0.00001$). Conclusions: The overall data of the shown meta-analysis suggested that the expression of SIRT1 is correlated with cancer risk cancer drug resistance.

Keywords: SIRT1, Cancer, Drug Resistance, Clinicopathological Characteristics, Meta-Analysis

Introduction

The past few decades have seen significant progress in our understanding of cancer reasons as well as advances in early detection, treatment, and prevention, which have led to declining cancer mortality in the industrialized world.[1, 2] Despite this progress, certain cancers continue to increase in different parts of the world, and cancers are among the most threat to death.[3]There are now surgical treatments, chemotherapy and radiotherapy for tumors. Surgery excision is the main treatment for precancerous tumor, but the curative effect of the surgery is poor, and the rate of recurrence is high. Advanced and recurrent cancers are no longer suitable for hand surgery, so drug therapy is necessary to prevent cervical cancer from progress and recurrence. But now the biggest obstacle to the treatment of recurrent and advanced cancer is tolerance to chemotherapeutic drugs.[4, 5] To overcome the resistance of cancers to drugs, the research of a novel drug resistance mechanism has the uncommonly important scientific meaning and the clinical value. Sirtuins, a highly conserved protein family, has been shown to be a significant protease partaking in the cancers drug resistance.[6]

Sirtuin 1 (SIRT1) is 1 of 7 members of the sirtuin family of nicotinamide adenine dinucleotide (NAD⁺)-dependent class III histone deacetylase that are human homologues of yeast silent mating-type

information regulator 2 (sir2).[6, 7] It mediates the deacetylation of various substrates including p53, FOXO, peroxisome proliferator activated receptors co-activator 1 α (PGC1 α) and other proteins, and thus regulates diverse physiological processes including aging, genomic stability and metabolism.[8, 9] Therefore, SIRT1 is a multifunctional protein that plays a central role in various pathways. A large number of studies have confirmed that SIRT1 is involved in tumorigenesis and development, and more studies have reported that SIRT1 is closely related to the process of drug resistance in tumors.[10-14] However, its role in tumor drug resistance is ambiguous. In this study, we conducted a meta-analysis of published studies to estimate the prognostic and clinicopathological value of SIRT1 in tumor drug resistance. The clinical significance of the findings were also discussed.

Materials and Methods

Search strategy and study selection

To get access to potentially eligible studies, we conducted an thorough electronic search for relevant studies using PubMed, Embase, Web Of Science(WOS) (up to September, 2018) with no restriction of origin or language, using various combinations of the following terms: “SIR2L1 protein, human” or “sirtuin1, human” or “Sir2-like1 protein, human” or “sirtuin (silent mating type information regulation 2 homolog) 1 (S. cerevisiae), human” or “SIRT1 protein, human” (title

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and abstract) and neoplasia or neoplasm or tumor or cancer or malignancy (title and abstract) and “Resistance, Drug” or “Drug Resistance” (title and abstract). The reference lists of relevant articles were searched manually as well.

Publications were considered eligible in our quantitative meta-analysis when they met all of the following criteria: (1) The diagnosis of cancers drug resistance was tested by using certain concentrations chemicals to the cancers; (2) SIRT1 expression was determined by immunohistochemistry(IHC) in the tissues of different cancers; (3) Sufficient information of the correlation of SIRT1 with clinicopathological features or overall survival time was provided to estimate odds ratio (OR) and hazard ratio (HR); (4) Being written as full papers; studies were excluded on the basis of the following criteria: (1) duplicate or overlapping populations; (2) lack of enough statistical data for further quantification analyses; (3) review articles, letters or case reports; (4) All evaluations were independently conducted by two authors to ensure the accuracy of the selection process.

Data extraction and quality assessment

To decrease bias and improve reliability, all data were extracted by two independent reviewers using a standardized data abstraction tool. when a discrepancy arose, a third reviewer was consulted to resolve the dispute. For all eligible studies, the following data was extracted: name of the first author, year of publication, country, number of cases, method, Clinicopathological characters, cancer type If the articles had Kaplan-Meier curves, Engauge Digitizer V4.1 (<http://digitizer.sourceforge.net/>) was used to digitize and collect survival data.

Statistical analysis

Odds ratios (ORs) and their 95% confidence intervals (CIs) were used to assess correlations between SIRT1 expression and the clinicopathological features of cancer drug resistance. In these analyses, $P < 0.05$ was considered significant. All analyses were performed using RevMan 5.3 software (Cochrane Collaboration, <http://community.cochrane.org/tools/review-production-tools/revman-5/revman-5-download>). Heterogeneity among studies was evaluated using the chi-squared-based Q-test and the I^2 test. P value higher than 0.05 for the Q test and I^2 value less than 50% were considered to be of no noteworthy heterogeneity, the fixed effects model was adopted ($P > 0.05$, $I^2 < 50\%$); If not, the random effects model was applied. The publication bias was evaluated by funnel plot. All the statistical tests were two-sided, and $P < 0.05$ was considered as statistically significant publication bias. All P values were 2-tailed.

Results

Study selection and characteristics

Initially, 7 articles were identified by searches of the

PubMed, Embase, Web of Science, databases using the strategy described above.[10, 15-20] Firstly, 1100 obvious irrelevance records were excluded. After reviewing the titles and abstracts, 70 studies were excluded. Because of duplication, irrelevancy, or non-originality (e.g., reviews, letters), The remaining 38 studies were reviewed in detail because of duplication, irrelevancy, or non-originality (e.g., reviews, letters), the most articles were excluded. Finally, seven articles were included in the current meta-analysis. A flow chart of the included studies is shown in Figure 1. All of these 7 included studies were only evaluated by immunohistochemistry (IHC) method. The expression of SIRT1 was observed only in the nucleus, while it can be expressed both in cytoplasm and nucleus. The participants in all the literatures were categorized into high SIRT1 expression group and low SIRT1 expression group. Main characteristics of detailed features of the clinical samples were summarized in Table 1.

Sensitivity analyses

There are 7 studies investigated the relationship between SIRT1 expression and cancer drug resistance with a total number of 790 patients diagnosed with different cancers. Our calculations showed that higher Sirt1 expression indicated the cancers were more resistant to some chemotherapeutics for solid malignancies, (OR=7.99, 95% CI: 5.70–11.21, $P < 0.00001$ Figure 2). Furthermore, subgroup analysis showed a concordant trend. For example, lung cancer (OR=7.97, 95% CI: 4.66–10.63) in Table 2.

Publication bias

We used funnel plots to visualize publication bias by RevMan 5.3.(Figure 3)

Discussion

SIRT1, homologue of the yeast Sir2 protein, is the best characterized member within the family of sirtuins with regard to life span and age-related disease. SIRT1 is expressed in many cells and was originally identified as a nuclear protein.[21] However, recent studies showed that subcellular localization of SIRT1 differs from cell to cell. SIRT1 is involved in DNA damage repair, cell cycle, apoptosis and oxidative stress in normal cells. While for tumor cells, SIRT1 has an anti-apoptotic effect and thus promoting carcinogenesis. Overexpression of SIRT1 has been found in a variety of solid tumors. Recently, some studies focus on the relationship between SIRT1 expression and efficacy of chemotherapy.[22-25]

While the improvement in living standards, changes in lifestyle and dietary structure, the incidence of cancer still has been increasing. Coupled with the current prevalence of cancer resistance, it is particularly important to find new treatments. Based on a large number of literature reports, we selected SIRT1 as the gene we studied, and analyzed the relationship between

SIRT1 and tumor resistance. In our analysis, we found that the Patients with high SIRT1 expression had a significantly higher chance to be resistant to chemotherapy than those with low SIRT 1 expression. In support of an negative role of SIRT1 in comprehensive cancer, Chen and co-workers[12] recently observed higher levels of SIRT1 can promote the development and drug resistance of hepatoma cells. Mao reported SIRT1 regulates YAP2-mediated cell proliferation and chemoresistance in hepatocellular carcinoma. On the other hand, a large amount of studies had tested SIRT1 had the indirect effect on the cancer drug resistance.[26, 27] SIRT1 can be the targets of many proteins and it participates in autophagy, apoptosis, DNA damage and the synthesis of drug-resistant proteins are involved in the formation of tumor resistance.

In our meta-analysis, 7 studies containing 790 cancer patients' tissue were included. Our data showed that SIRT1 over-expression was significantly associated with cancer drug resistance. The above findings indicated that SIRT1 might act as a novel oncogene, which might be effective to predict the prognosis of tumor chemotherapy effect.

To the best of our knowledge, our present meta-analysis is the first study to explore the potential relationship between SIRT1 expression and cancer drug resistance. However, some limitations of our meta-analysis should be noted. Firstly, we only included 7 studies (including lung cancer, endometrial carcinoma, esophageal squamous cell carcinoma, breast cancer, gastric cancer, colorectal cancer, ovarian cancer). Besides, the studies distributed mainly about Asian countries, and mostly researches from China. Attributed to the small number of included studies, we failed to conduct a subgroup analysis of OS based on the follow up period. Hence, the association of SIRT1 expression with overall survival time still needs to be studied in a larger number of samples. Finally, owing to most of the cases in the literatures are relatively small, the heterogeneity among the studies remained, despite the usage of a random-effects model and subgroup analyses. The heterogeneity could have generated outcome bias.

In spite of the flaws mentioned above, there is plenty of pragmatic value in our study. Our meta-analysis indicates a positive association between the over-expression of SIRT1 with cancers drug resistance. In addition, SIRT1 may be used as a biomarker to predict unfavorable reproductive cancer prognosis

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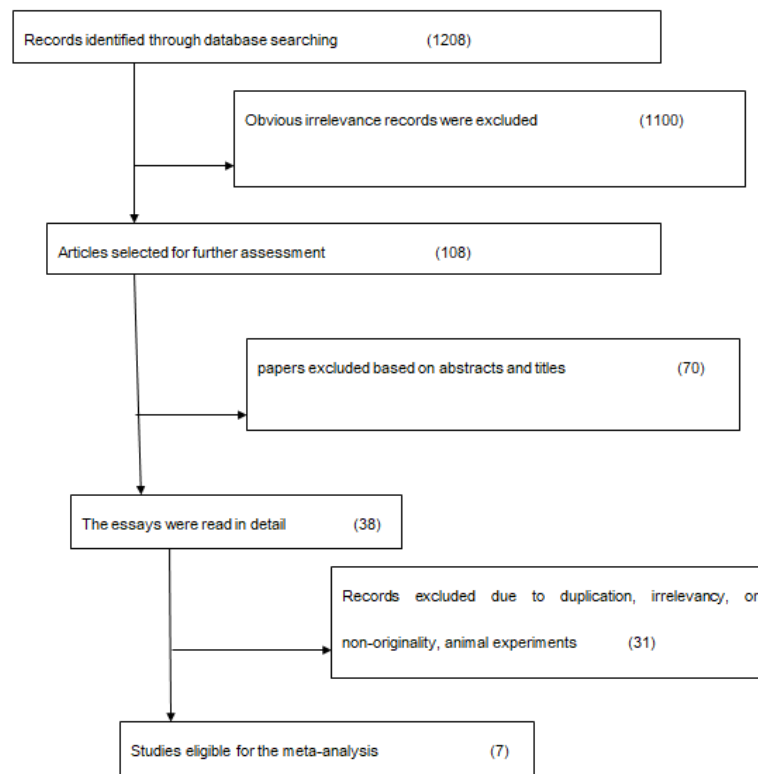


Figure 1: The steps for screening eligible publications for the meta-analysis.

Table 1: Characteristics of the included studies in this meta-analysis

Author	Year	Country	Cancer type	Case	Method	FIGO grade	High sirt1/Low sirt1
Zhang	2013	China	lung cancer	295	IHC	III (A+B) +IV	137/48
Asaka	2015	Korea	endometrial carcinoma	108	IHC	I+II+III+IV	58/7
Cao	2014	China	esophageal squamous cell carcinoma	68	IHC	I+II+III+IV	25/3
Lin	2014	Japan	breast cancer	122	IHC	I+II+III+IV	78/9
Zhang	2013	China	gastric cancer	24	IHC	NA	15/2
Shuang	2015	China	ovarian cancer	63	IHC	I+II+III+IV	18/10
Wang	2018	China	colorectal cancer	110	IHC	II+III	51/12

Table 2: Shows the association between the SIRT 1 expression and chemotherapy response status of lung cancer

SIRT1 expression	Non-responder	%	responder	%	OR	95%CI	P
High SIRT1	137	74.05	29	26.36	1.00		
Low SIRT1	48	25.95	81	73.64	7.97	4.66 - 10.63	< 0.001

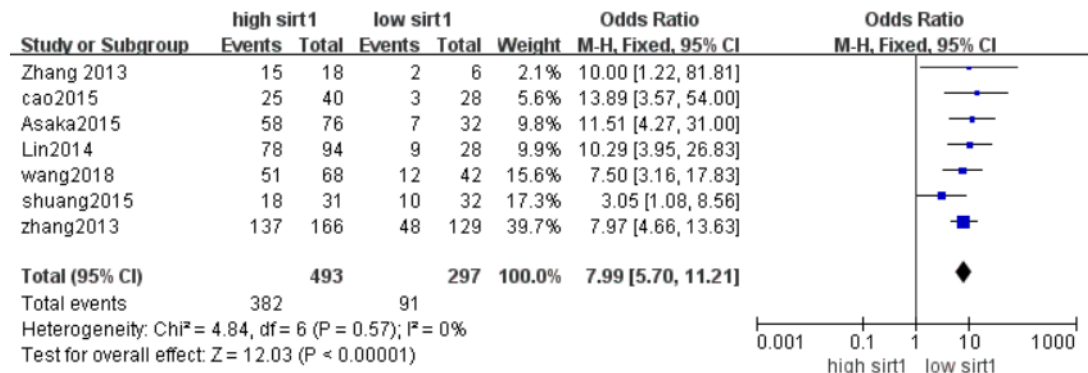


Figure 2. Forest plots of associations between SIRT1 expression with the risk of cancer drug resistance.

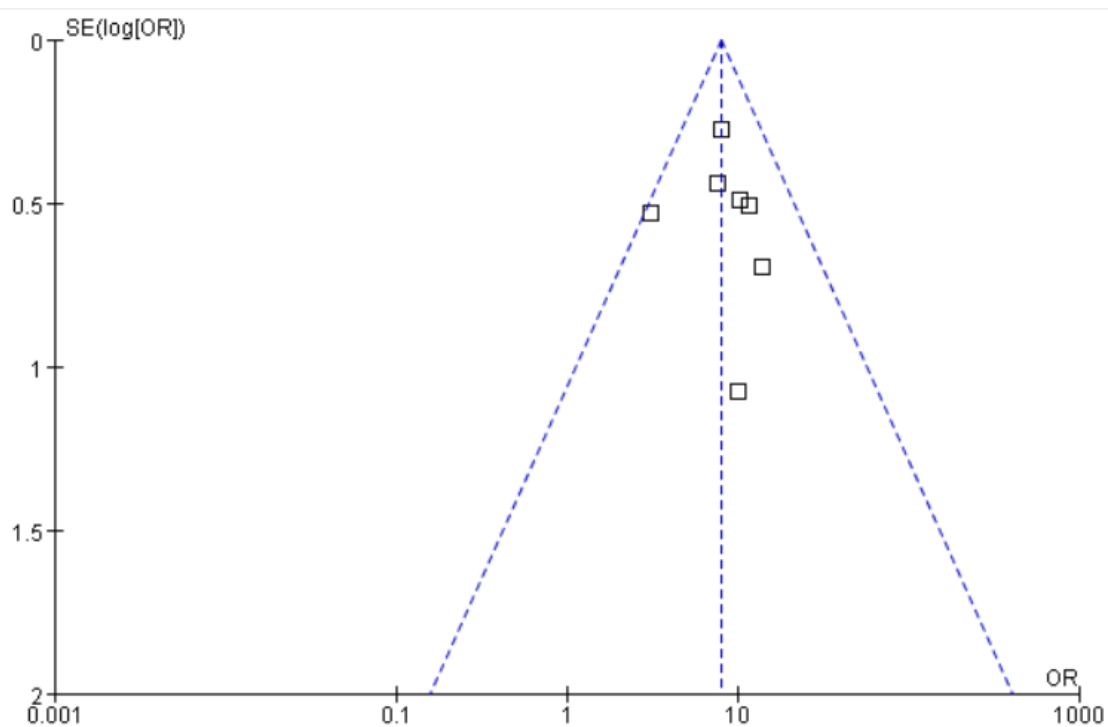


Figure 3: The funnel plots of OS for this meta-analysis