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Review Article

Altered Sirtuin1 and Sirtuin6 Expression in Aging: A Systematic Review and Meta-Analysis

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Abstract

The sirtuin family, comprising nicotinamide adenine dinucleotide-dependent deacetylases, is involved in diverse physiological functions in mammals. Sirtuin 1 (SIRT1) and 6 (SIRT6) are involved in age-related biological processes, primarily in deacetylating metabolic stability and DNA repair-related factors. The expression patterns of SIRT1 and SIRT6 in aging remain controversial. Therefore, we performed a meta-analysis to evaluate the expression patterns of SIRT1 and SIRT6 in aged humans and rodents. Twenty-five studies (n = 1,417) were included to analyze SIRT1 expression, and three studies (n = 312) were included to analyze SIRT6 expression in aging. Meta-analysis showed that SIRT1 expression decreased (n = 1,208) (standard mean difference [SMD]=-0.46; 95 % confidence interval [CI]: -1.89 to 0.97; P < 0.00001) in humans, while increased in rodents (n = 209) (SMD=2.38; 95 % CI: -0.22 to 4.97; P < 0.00001). SIRT6 expression showed consistently decreased tendency (SMD=-11.04; 95 % CI: -17.73 to -4.36; P < 0.00001) in the aging group compared with to the young group. Especially, subgroup analysis for the brain area also showed a decrease in SIRT6 expression in all included studies. This systematic review and meta-analysis proposes a various and comprehensive understanding of SIRT1 and SIRT6 expression during normal aging.

INTRODUCTION

Sirtuins (mammalian silent mating-type information regulation 2 homologs; SIRT) are a class of nicotinamide adenine dinucleotide (NAD+)-dependent enzymes that belong to a family of histone deacetylases [1,2]. SIRT is a longevity regulator mediating DNA repair, chromatin remodeling, and genomic stability [3-6]. There are seven isoforms of SIRTs in mammals (SIRT1-7) with different subcellular localizations and functions. Notably, SIRT1 and SIRT6 are mainly located in the nucleus and play a key role in age-associated pathophysiologies in mammals by maintaining metabolism stability [7-10]. SIRT1 and SIRT6 are abundantly expressed in the brain, and their expression patterns change as aging progresses [11,12].

SIRT1 expression decreases with increasing age and is related to metabolic and aging-related diseases regulating micro-RNA (miR)-134 or miR-34a [10,12-17]. Meanwhile, it has also been demonstrated that SIRT1 expression increases mainly to resist age-related oxidative stress [18-21]. Moreover, a few studies indicate that SIRT6 expression decreases with aging, which increases the acetylation of histone H3 lysine-9 (H3K9) and histone H3 lysine-56 (H3K56) [8]. Considering these recent trends in aging-related research, altered SIRT1 and SIRT6 expression can be closely related causes of aging-associated diseases. Therefore, establishing the expression pattern of SIRT1 and SIRT6 in an aging group can provide a basis for understanding various aging-related mechanisms and diseases.

Thus, we conducted a meta-analysis to clarify the relationship between normal aging and SIRT1 and SIRT6 expression in humans and rodents. In addition, we meta-analyzed SIRT1 and SIRT6 expression in the brain.

MATERIAL AND METHODS

Publication search for systematic review

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) guidelines. We conducted an electronic literature search using two electronic databases (PubMed and

Web of Science) to collect data from December 1995 to July 2021. For the initial data search, the publications were retrieved using key terms, including "sirtuin1" or "sirt1" or "sirtuin6" or "sirt6." After the literature search, we carefully screened and selected appropriate publications.

Eligibility criteria (inclusion/exclusion criteria)

The inclusion criteria of this meta-analysis are described as follows: (1) Articles written only in English; (2) In the case of animal studies, only rodents were included, with species and age (or weight) mentioned; (3) In the case of human studies, the age was exactly stated; (4) Measurement methods and numeric data of SIRT1 and SIRT6 expression were specified; (5) The studies were written according to a possible population, intervention, comparison, and outcome (PICO) approach; and (6) The full text of the studies could be obtained. In this meta-analysis, the PICO approach conditions were as follows: Participants, humans and rodents; intervention, normal aging; and comparison, young vs. aging conditions. The outcome was the quantification of SIRT1 or SIRT6 expression.

The exclusion criteria of this meta-analysis are described as follows: (1) Review, duplicate studies, and articles not written in English; (2) In the case of animal studies, genetically modified animals and disease models; (3) In the case of human studies, patients diagnosed with a disease; (4) Unclear and inaccessible measurement methods and numeric data of SIRT1 and SIRT6 expression; and (5) The full text of the studies could not be accessed.

Data extraction and statistical analysis

The included studies were sorted based on title-abstract-full text screening. Studies with mean and standard deviation reported were included for meta-analysis. Two authors independently conducted data screening and extraction. The following study characteristics were collected based on the previously described strategy [22]. Briefly, the main characteristics included the name of the first author and year of publication, species, sex, age or weight, measured area, and assessment methods. Review manager version 5.3 software (Revman 5.3, Copenhagen, Denmark) was used for meta-analysis. The relationship between normal aging and SIRT1 or SIRT6 expression was analyzed using a comparison with 95% confidence interval (CI) with the random-effect model. The outcomes of the included studies were analyzed using the standard mean difference (SMD). We assessed the heterogeneity between study results by calculating I2 statistics.

Assessment of risk of bias and publication bias

To assess the risk of bias in the selected publications, we used Revman 5.3 program [Figure 1]. Two authors independently evaluated each risk of bias across all included studies. The publication bias of this meta-analysis was evaluated using a funnel plot. Funnel plots of the SMD are plotted against the standard error (SE).

RESULTS

Study selection

In the initial stage, a total of 23,998 studies were identified. After the duplication test, 11,053 studies were excluded. The remaining 12,945 studies were carefully screened at the title and abstract level; 2,989 and 5,679 studies were excluded based on their title and abstract, respectively. Next, 4,277 studies were evaluated at the full-text level; 4,066 studies were excluded, and 211 studies were assessed for eligibility. Finally, 28 studies were included in this meta-analysis based on the eligibility criteria. A PRISMA flow diagram for the selection and sorting process of included studies is presented in Figure 2. The comparisons of outcomes were separated according to the sirtuin type (SIRT1 or SIRT6).

Characteristics of the included studies

We conducted two meta-analyses according to the sirtuin types (SIRT1 or SIRT6). Major characteristics of the included studies in the two meta-analyses are represented in Table I and Table II, respectively. The characteristics included species, sex, the number of groups, age (weight), measured area, and assessment method. In the case of the meta-analysis about SIRT1 expression in normal aging, 25 studies were included. This analysis comprised 14 human studies and 11 rodent studies. Of the total 25 studies, 10 studies measured SIRT1 in the blood [20,23-31], 5 studies measured SIRT1 in the brain [12,32-35], and the remaining 10 studies measured SIRT1 in other tissues [32,36-45]. Since one study measured SIRT1 in the blood and other tissues, data and characteristics were recorded separately [32] [Table 1].

In the case of meta-analysis of SIRT6 expression in normal aging, 3 studies were included, two of which were human studies and one was an rodents study. Of the included studies, two measured SIRT6 in the brain [12,32] and two studies measured SIRT6 in other tissues [32,36]. Since one study measured SIRT6 in the blood and other tissues, data and characteristics were recorded separately [32] [Table 2].

Meta-analysis of SIRT1 and SIRT6 expression in aged humans and rodents

We conducted a meta-analysis for each sirtuin type to evaluate the trend of SIRT1 and SIRT6 expression in aging. SIRT1 expression increased in the aging group (n = 691) compared with that in the young group (n = 726) (SMD = 0.40; 95% CI, -0.77 to 1.57; P < 0.00001) [Figure 3A]. However, the expression of SIRT6 remarkably decreased in the aging group (n = 146) compared with that in the young group (n = 166) (SMD = -11.04; 95% CI, -17.73 to -4.36; P < 0.00001) [Figure 3B]. The heterogeneity for each meta-analysis was measured using I2. The heterogeneity of both meta-analyses was I2 = 98%. A funnel plot was used to evaluate the publication bias of the literature. The funnel plot of the studies included in the meta-analysis of SIRT1 expression in normal aging revealed symmetric but a linear shape [Figure 4A]. The meta-analysis of SIRT6 expression showed a little asymmetry [Figure 4B].

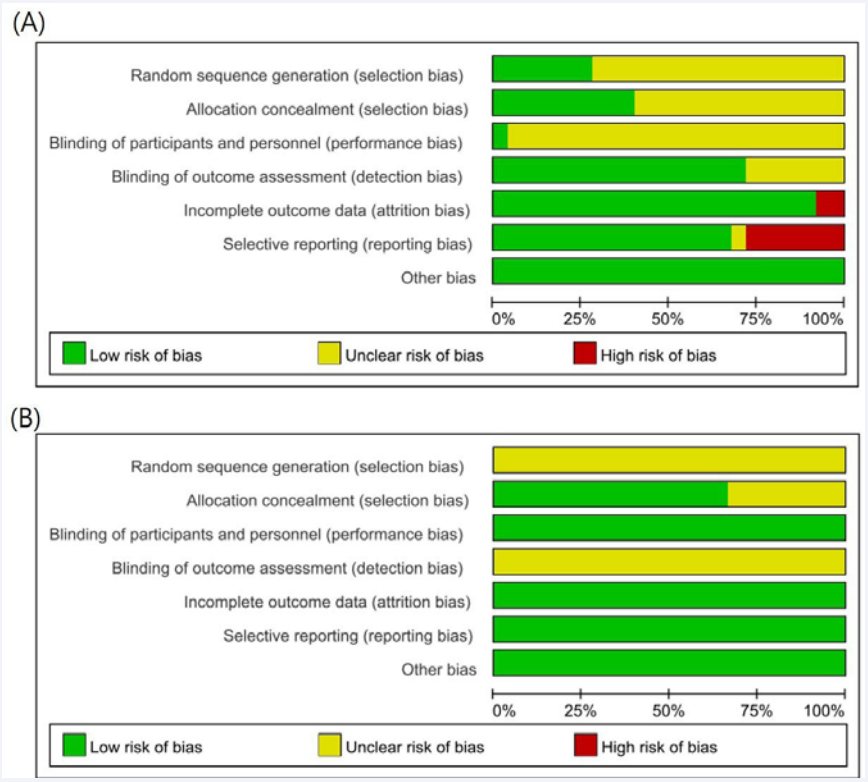

Figure 1 Risk of bias list chart from the included studies. **(A)** Risk of bias chart of the selected total studies on SIRT1 expression in normal aging. **(B)** Risk of bias chart of the selected total studies on SIRT6 expression in normal aging.

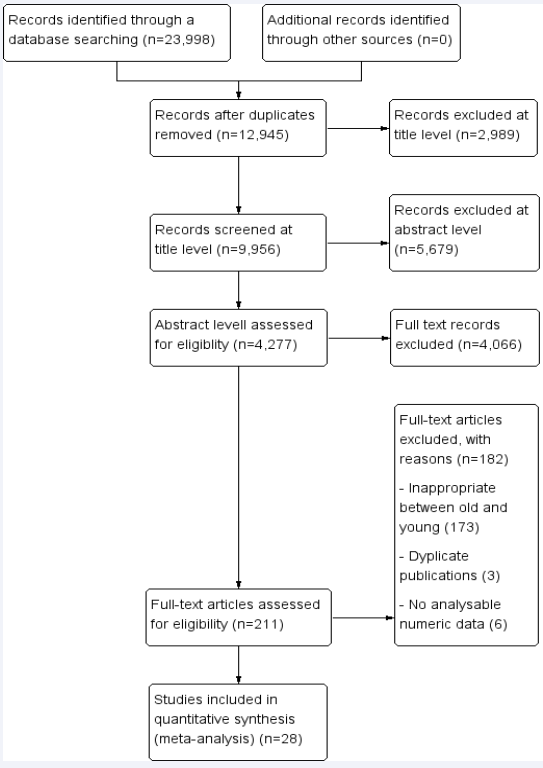

Figure 2 PRISMA flow diagram for selection and sorting of the included studies.

Table 1: Main characteristics of included studies on the expression of SIRT1 in normal aging

	Study	Species	Gender	Age or weight	Measured area	Measuring method
1	Wojciak G et al. 2020	Human	M	Young: 21.5 ± 0.5 years (n = 10) Old: 61.5 ± 6.5 years (n = 10)	Blood	ELISA
2	Caldeira CA et al. 2021	Human	-	Young: 52.1 ± 4 years (n = 10) Old: 76.3 ± 7 years (n = 13)	Blood	Chemi-luminescence
3	Opstad TB et al. 2020	Human	M (n = 50) FM (n = 68)	Young: 29 ± 11 years (n = 51) Old: 66 ± 15 years (n = 66)	Blood	PCR
4	Wongchitrat P et al. 2019	Human	Young: M (n = 29) FM (n = 11) Old: M (n =26) FM (n = 14)	Young: 28.8 ± 0.7 years (n = 40) Old: 68.5 ± 1.1 years (n = 40)	Blood	PCR
5	Lee HJ et al. 2017	Human	M	Young: 20's (n = 18) Old: 60's (n = 25)	Blood	Sirt1 assay kit
6	Zhong Y et al. 2015	Human	Young: M (n = 21) FM (n = 9) Old: M (n =17) FM (n = 13)	Young: 18.98 ± 0.89 years (n = 30) Old: 73.83 ± 5.1 years (n = 30)	Blood	ELISA
7	Wang Y et al. 2015	Human	-	Young: 25.5 ± 4.5 years (n = 29) Old: 51.5 ± 4.5 years (n = 31)	Blood	ELISA
8	Kilic U et al. 2015	Human	Young: M (n = 103) FM (n = 12) Old: M (n = 67) FM (n = 36)	Young: 46.9 ± 0.5 years (n = 115) Old: 73.5 ± 1.0 years (n = 103)	Blood	ELISA
9	Kumar R et al. 2014	Human	Young: M (n = 69) FM (n = 50) Old: M (n = 52) FM (n = 29)	Young: 68.41 ± 3.5 years (n = 119) Old: 74.34 ± 6.59 years (n = 81)	Blood	BIAcore 2000
10	Kumar R et al. 2013	Human	Young: M (n = 11) FM (n = 11) Old: M (n = 13) FM (n = 9)	Young: 26.68 ± 3.77 years (n = 22) Old: 72.5 ± 5.62 years (n = 22)	Blood	ELISA
11	Pukhalskaia AE et al. 2020	Human	-	Young: 63.0 ± 2.4 years (n = 58) Old: 82.0 ± 2.3 years (n = 58)	Brain (Hippocampus)	IHC
12	Spirichev AA et al. 2020	Wistar rats	M+FM (n = 20)	Young: 2 months Old: 24 months	Brain (Hypothalamus)	WB
13	Singh S et al. 2017	Wistar rats	M	Young: 4 months (n = 6) Old: 24 months (n = 6)	Brain	PCR
14	Wong DW et al. 2015	C57BL/6N mice	M	Young: 4 months (n = 9) Old: 24 months (n = 10)	Brain (Preoptic area)	PCR
15	Braidy N et al. 2015	Wistar rats	FM	Young: 3 months (n = 8) Old: 12 months (n = 8)	Brain (Hippocampus)	PCR
16	Carbone A et al. 2020	Human	Young: M (n = 18) FM (n = 24) Old: M (n = 5) FM (n =17)	Young: 45.3 ± 4.3 years (n = 42) Old: 92.1 ± 1.7 years (n = 22)	Buccal epithelium	PCR
17	Pukhalskaia AE et al. 2020	Human	-	Young: 63.0 ± 2.4 years (n = 58) Old: 82.0 ± 2.3 years (n = 58)	Saliva	ELISA
18	Liao FX et al. 2021	Human	Young: M (n = 5) FM (n = 1) Old: M (n = 4) FM (n =2)	Young: 27.5 ± 5.9 years (n = 6) Old: 60.5 ± 3.8 years (n = 6)	Knee cartilage	IHC
19	Massudi H et al. 2012	Human	-	Young: 41.17±1.88years (n = 12) Old: 63.17±1.31 years (n = 23)	Pelvic region skin	Sirt1 assay kit
20	Sanchez-Roman I et al. 2012	Wistar rats	M	Young: 6 months (n = 4-8) Old: 24 months (n = 4-8)	Liver	WB
21	Donato AJ et al. 2011	B6D2F1 mice	M	Young: 5-7 months (n = 16) Old: 30 months (n = 14)	Aorta	WB
22	Machida S et al. 2004	F1 generation of Fisher 344× Brown Norway rats	M	Young: 3 months (n = 5) Old: 30 months (n = 5)	Muscle	WB
23	Ferrara N et al. 2008	Wistar rats	M	Young: 6 months (n = 10) Old: 24 months (n = 10)	Heart	Sirt1 assay kit
24	Zeng Y et al. 2015	Sprague-Dawley, (SD) rats	M	Young: 1 months (n = 8) Old: 19 months (n = 8)	Retina	WB
25	Huang CC et al. 2016	Sprague-Dawley, (SD) rats	M	Young: 3 months (n = 8) Old: 12 months (n = 6)	Gastrocnemius muscles	WB
26	Xiu C et al. 2020	Sprague-Dawley, (SD) rats	-	Young: 2 months (n = 10) Old: 18 months (n = 10)	Lens	WB

ELISA: Enzyme-linked immunosorbent assay; FM: Female; IHC: Immunohistochemical staining; M: Male; PCR: Polymerase chain reaction; WB: Wester blotting

Table 2. Main characteristics of included studies on the expression of SIRT6 in normal aging

	Study	Species	Gender	Age or weight	Measured area	Measuring method
1	Pukhalskaia AE et al. 2020	Human	-	Young: 63.0 ± 2.4 years (n = 58) Old: 82.0 ± 2.3 years (n = 58)	Brain	IHC
2	Pukhalskaia AE et al. 2020	Human	-	Young: 63.0 ± 2.4 years (n = 58) Old: 82.0 ± 2.3 years (n = 58)	Saliva	ELISA
3	Braidy N et al. 2015	Wistar rats	FM	Young: 3 months (n = 8) Old: 24 months (n = 8)	Brain	PCR
4	Carbone A et al. 2020	Human	M (n =18) FM (n =24)	Young: 45.3 ± 4.3 year (n = 42) Old: 92.1 ± 1.7 years (n = 22)	Buccal epithelium	PCR

ELISA: Enzyme-linked immunosorbent assay; FM: Female; IHC: Immunohistochemical staining; M: Male; PCR: Polymerase chain reaction

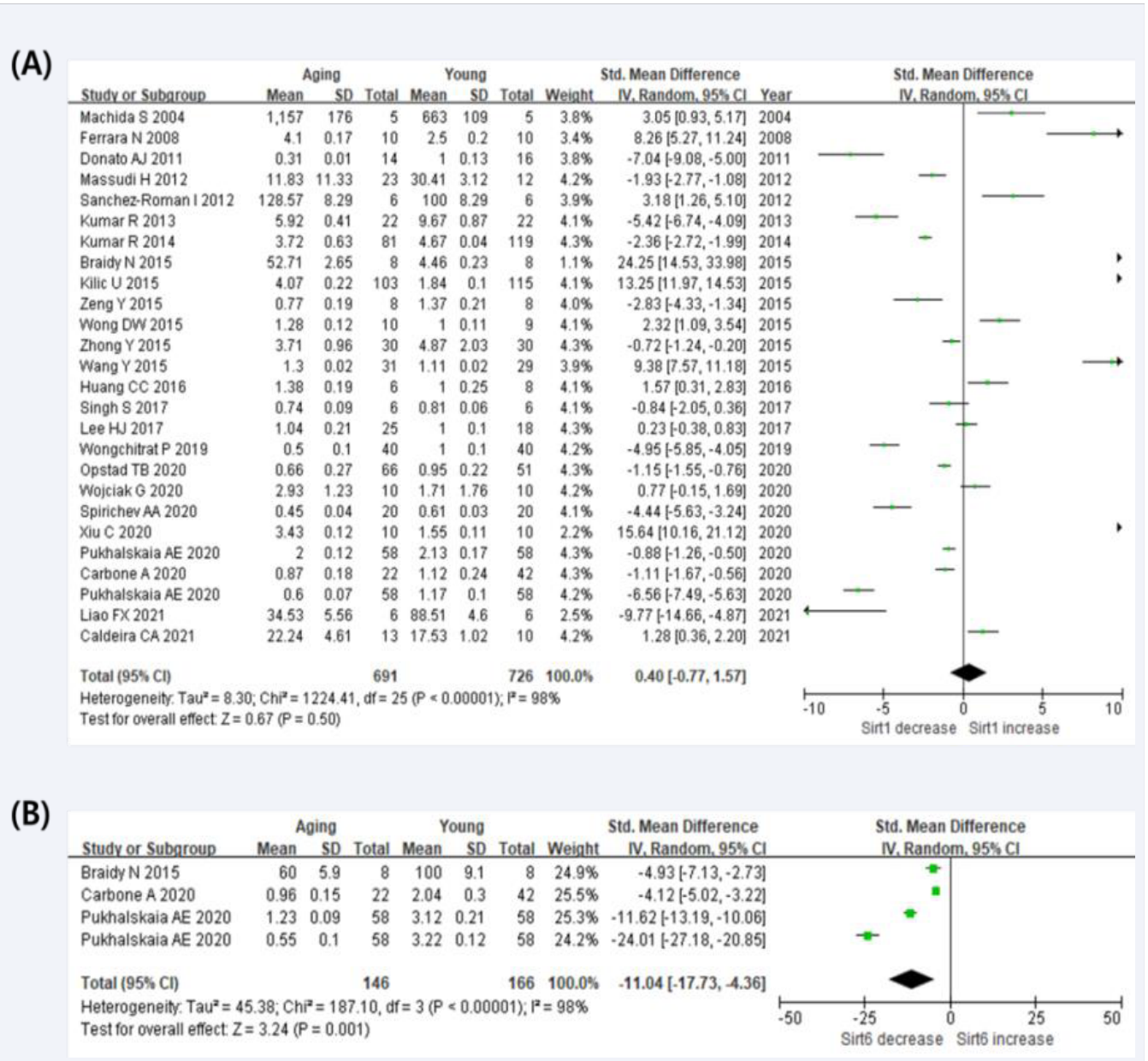

Figure 3 Forest plots of the meta-analysis of SIRT1 and SIRT6 expression in the aging group.
(A) Forest plot showing the trend of SIRT1 expression in the aging group compared to that in the young group.
(B) Forest plot showing the trend of SIRT6 expression in the aging group compared to that in the young group.
Abbreviations: SMD: Standardized Mean Difference; IV: Independent Variable; CI: Confidence Interval

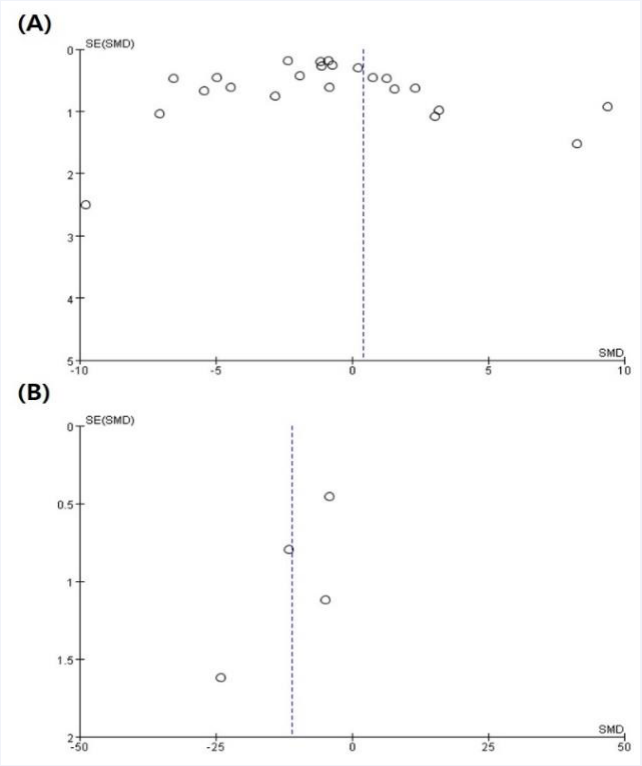

Figure 4 Evaluation of publication bias using funnel plots for all the studies included in the meta-analysis. **(A)** A funnel plot showing the publication bias for the included studies in the meta-analysis of SIRT1 expression in the aging group. **(B)** A funnel plot showing the publication bias for the included studies in the meta-analysis of SIRT6 expression in the aging group.
Abbreviations: SE: Standard Error; SMD: Standardized Mean Difference

Subgroup analysis of SIRT1 expression in aged humans and rodents

To compare SIRT1 expression pattern between species, subgroup analysis was conducted in the human group and the rodent group, respectively. SIRT1 expression in humans decreased in the aging group (n = 588) compared with that in the young group (n = 620) (SMD = -0.46; 95% CI, -1.89 to 0.97; P < 0.00001) [Figure 5A]. In rodents, SIRT1 expression increased in the aging group (n = 103) compared than young group (n = 106) (SMD = 2.38; 95% CI, – -0.22 to 4.97; P < 0.00001) [Figure 5A]. The heterogeneity for subgroup-analysis of humans and rodents group was I2 = 99% and I2 = 96%, respectively. The funnel plot for the included studies showed a more symmetric bell shape than the total meta-analysis when conducting subgroup analysis [Figure 5B].

Meta-analysis of SIRT1 and SIRT6 expression in the brains of aged humans and rodents

To evaluate the expression trend of SIRT1 and SIRT6 in the aging brain, we performed meta-analyses in which the measured area was the brain. The expression of SIRT1 increased in the aging group (n = 102) compared with that in the young group (n = 101) (SMD = 0.28; 95% CI, – 2.13 to 2.70; P < 0.00001) [Figure 6A]. This trend is consistent with increased SIRT1 expression measured in the blood and other tissues. In addition, the trend of SIRT6 expression decreased in the aging group (n = 66) compared with that in the young group (n = 66) (SMD = -11.67; 95% CI, -13.16 to -10.18; P = 0.85) [Figure 6B]. This trend is consistent with SIRT6 expression patterns in the blood and other tissues. The heterogeneity for meta-analysis of SIRT1 and SIRT6 expression was I2 = 95% and I2 = 0%, respectively. Funnel plots of each analysis are shown in Figures 6C and 6D [Figure 6C and 6D].

DISCUSSION

The SIRT family, consisting of NAD+-dependent histone deacetylases, regulates various physiological functions, such as DNA repair and chromatin remodeling [46]. Recent studies have indicated that SIRT1 and SIRT6 are closely associated with aging-related cellular or neuronal changes primarily through the deacetylation of transcription factors and co-factors [10,47].

The age-related regulatory mechanism of SIRT1 is dependent on the NAD+ level, which regulates the expression of several oxidative stress and inflammation-related transcription factors (Nrf-2, FOXOs, and NF-κB), poly (ADP-ribose) polymerase, and hormones (such as insulin-like growth factor 1 [IGF1]) [10,11]. Interestingly, age-related diseases, such as neurodegenerative and cardiovascular diseases, can be induced by a decrease in NAD+, which is mediated by a decrease in SIRT1 [17].

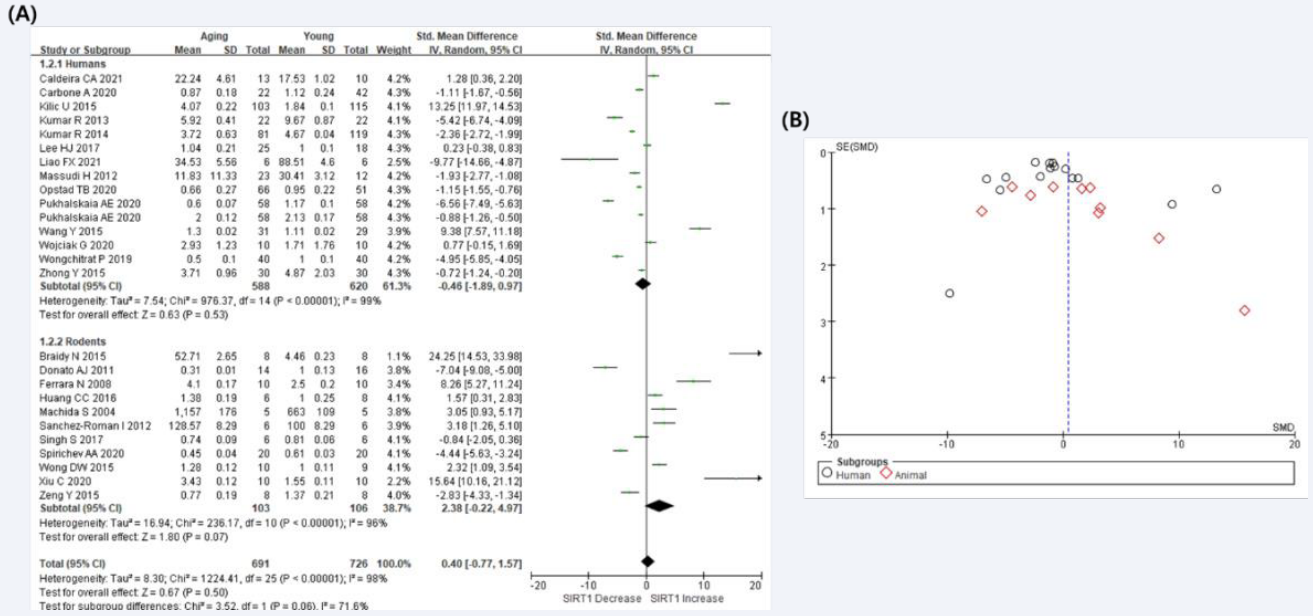

Figure 5 Forest plot and funnel plot of the subgroup analysis of SIRT1 expression in the aging group.
(A) Forest plot showed the trend of SIRT1 expression between the humans and rodents aging groups compared to that in the young group.
(B) Funnel plot showing the publication bias for the included studies in the subgroup analysis of SIRT1 expression.
Abbreviations: SMD: Standardized Mean Difference; IV: Independent Variable; CI: Confidence Interval; SE: Standard Error

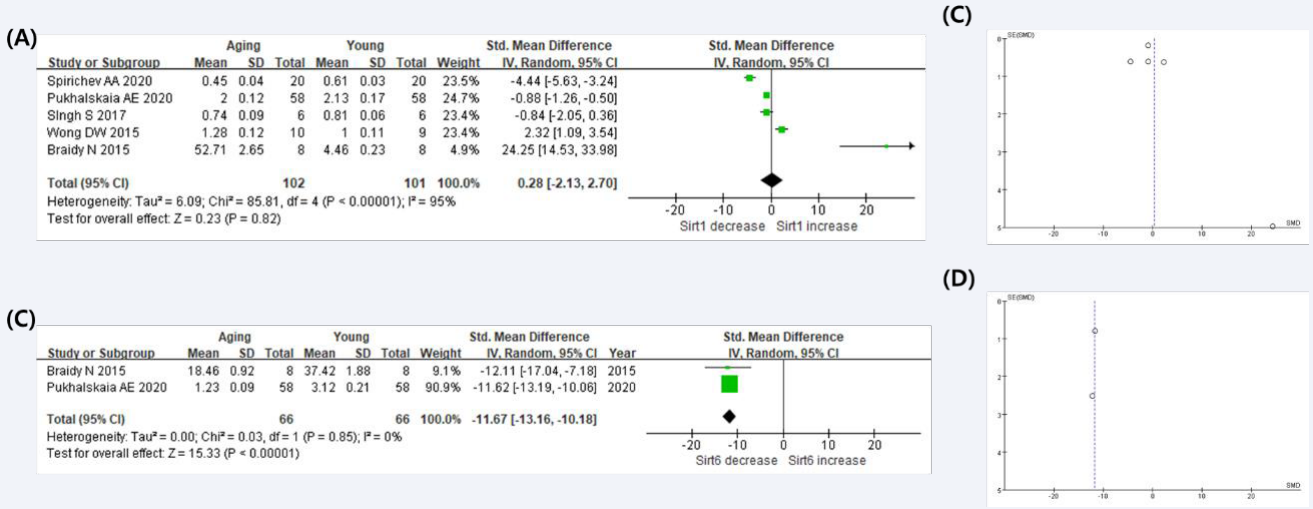

Figure 6 Forest plot and funnel plot of the meta-analysis of SIRT1 and SIRT6 expression in the brain of the aging group.
(A) Forest plot showing the trend of SIRT1 expression in the brain of the aging group compared to that in the young group.
(B) Forest plot showed the trend of SIRT6 expression in the brain of the aging group compared to that in the young group.
(C) Funnel plot showing the publication bias for the included studies in the meta-analysis of SIRT1 expression in the brain of aging group.
(D) Funnel plot showing the publication bias for the included studies in the meta-analysis of SIRT6 expression in the brain of aging group.
Abbreviations: SMD, Standardized Mean Difference; IV, Independent Variable; CI, Confidence Interval; SE, Standard Error

MiR-34a, another factor regulating SIRT1, is abundantly expressed in the aging body [16,48]. Aged endothelial cells express high levels of miR-34a and low levels of SIRT1 [49], and the aging-associated increase of miR-34a in neurons induces neuronal death through the downregulation of SIRT1 expression and upregulation of the mechanistic Target of Rapamycin (mTOR) signal pathway [50]. These findings suggest that the miR-34a/SIRT1 signaling pathway has an important role in aging-related dysfunction.

Age-related decline in SIRT1 leads to an increase in acetylated endothelial nitric oxide synthase, which leads to age-related vascular endothelial dysfunction [40]. In the brain, an aging-associated decrease in SIRT1 expression reduces the expression of claudin-5, one of the tight junction proteins, thereby increasing blood-brain barrier permeability [47]. These findings suggest that the SIRT1 signaling pathway is important in vascular aging.

Meanwhile, some studies suggest that an age-related increase in SIRT1 expression may be a compensatory mechanism to compete against oxidative stress. In the aging process, SIRT1 mainly represses oxidative stress by regulating PGC-1α, AMPK, and FOXO [20,23,44]. Moreover, a compensatory increase in SIRT1 can increase the levels of available NAD+ to repair age-related DNA injury [12,51]. Consistent with these results, our meta-analysis of total SIRT1 expression shows a slightly increased trend in the aging group. However, subgroup analysis shows different patterns between humans and rodents. A subgroup analysis of SIRT1 expression in rodent studies showed the same pattern of increase with aging as the total SIRT1 analysis. In contrast, SIRT1 expression in human tended to decrease in the aging group compared to the young group. This is the first meta-analysis to show that humans and rodents have different trends in SIRT1 expression with aging, although the results need to be followed up in future studies.

SIRT6 is involved in aging and aging-related disease by maintaining genomic stability and redox homeostasis [5]. In the aging process, an increase in acetylation of H3K9 due to a decrease in SIRT6 induces cellular senescence through genomic instability and abnormal maintenance of telomere function [8,52]. The decrease in SIRT6 also induces changes in oxidative stress and in the expression of inflammation-related transcription factors (Nrf-2, FOXM1, and NF-κB), thereby accelerating cellular and vascular senescence [11,53,54]. In addition, SIRT6 regulates aging by controlling the IGF1 signaling pathway [17,55]. As aging progresses, IGF1 expression increases due to an aging-related decrease in SIRT6 expression, which induces an increase in genetic instability and abnormal metabolism [46]. Our meta-analysis shows a decreased expression trend for SIRT6 in the aging group. We speculate that these SIRT6 expression changes in the aging group may show that SIRT6 is relatively vulnerable to various stress-related conditions appearing in the aging process.

Our analysis has limitations such as heterogeneity and publication bias. In each comparison showed large heterogeneities across included studies. The subgroup analyses to calibrate for heterogeneity also showed relatively high heterogeneity. Differences in experimental methods, such as measurement methods and scale, may have contributed to the high heterogeneity of included studies. If more studies are included in the future, the quality of the subgroup analysis and sensitivity analysis will improve. Publication bias in our meta-analyses was evaluated using a funnel plot. In the total meta-analysis of the SIRT1 expression, the plot had an almost symmetric but linear shape. This result indicates that some of the studies included in the analysis had small effect sizes. However, the plot of subgroup analysis showed a more funnel-shape than the total SIRT1 meta-analysis. These results indicate that the analysis quality is improved compared to the overall meta-analysis of SIRT1 when analyzed by dividing humans and rodents separately. Controversy over changes in SIRT1 expression during aging may stem from differences in trends in SIRT1 expression with age in clinical and animal studies. In the case of meta-analysis of SIRT6 expression, the shape of the funnel plot was slightly out of symmetry, indicating that there was moderate variance among included studies; this finding suggests that in the included studies in the meta-analysis, a few had large effect sizes [56]. We speculated that the small number of included studies and the variety of assessment methods might influence this variance.

CONCLUSIONS

This meta-analysis shows that SIRT1 expression decreases in humans but increases in rodents in the aging group. This result suggests, for the first time, that age-related changes in SIRT1 expression may differ between humans and rodents. In the case of SIRT6 expression, the expression tended to decrease in both aging groups despite the limitation of the small number of studies. Our analysis further clarifies that SIRT6 is closely related to normal aging, especially in the brain. Future studies and analyses are necessary to elucidate precise aging-related SIRT1 or SIRT6 expressional change.

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REFERENCES

1. Herskovits AZ, Guarente L. Sirtuin deacetylases in neurodegenerative diseases of aging. Cell Res. 2013; 23: 746-758.
2. Dai Y, Faller DV. Transcription Regulation by Class III Histone Deacetylases (HDACs)-Sirtuins. Transl Oncogenomics. 2008; 3: 53-65.
3. Herranz D, Munoz-Martin M, Canamero M, Mulero F, Martinez-Pastor B, Fernandez-Capetillo O, et al. Sirt1 improves healthy ageing and protects from metabolic syndrome-associated cancer. Nat Commun. 2010; 1: 3.
4. Watroba M, Szukiewicz D. Sirtuins at the Service of Healthy Longevity. Front Physiol. 2021; 12: 724506.
5. Raj S, Dsouza LA, Singh SP, Kanwal A. Sirt6 Deacetylase: A Potential Key Regulator in the Prevention of Obesity, Diabetes and Neurodegenerative Disease. Front Pharmacol. 2020; 11: 598326.
6. Klein MA, Denu JM. Biological and catalytic functions of sirtuin 6 as targets for small-molecule modulators. J Biol Chem. 2020; 295: 11021-11041.
7. Baur JA, Ungvari Z, Minor RK, Le Couteur DG, de Cabo R. Are sirtuins viable targets for improving healthspan and lifespan? Nat Rev Drug Discov. 2012; 11: 443-461.
8. Zhao Y, Bai X, Jia X, Lu Y, Cheng W, Shu M, et al. Age-related changes of human serum Sirtuin6 in adults. BMC Geriatr. 2021; 21: 452-0.

9. Satoh A, Stein L, Imai S. The role of mammalian sirtuins in the regulation of metabolism, aging, and longevity. Handb Exp Pharmacol. 2011; 206: 125-162.

10. Satoh A, Imai SI, Guarente L. The brain, sirtuins, and ageing. Nat Rev Neurosci. 2017; 18: 362-374.

11. Jesko H, Wencel P, Strosznajder RP, Strosznajder JB. Sirtuins and Their Roles in Brain Aging and Neurodegenerative Disorders. Neurochem Res. 2017; 42: 876-890.

12. Braidy N, Poljak A, Grant R, Jayasena T, Mansour H, Chan-Ling T, et al. Differential expression of sirtuins in the aging rat brain. Front Cell Neurosci. 2015; 9: 167.

13. Prozorovski T, Schulze-Topphoff U, Glumm R, Baumgart J, Schroter F, Ninnemann O, et al. Sirt1 contributes critically to the redox-dependent fate of neural progenitors. Nat Cell Biol. 2008; 10: 385-394.

14. Tiberi L, van den Ameele J, Dimidschstein J, Piccirilli J, Gall D, Herpoel A, et al. BCL6 controls neurogenesis through Sirt1-dependent epigenetic repression of selective Notch targets. Nat Neurosci. 2012; 15: 1627-1635.

15. Saharan S, Jhaveri DJ, Bartlett PF. SIRT1 regulates the neurogenic potential of neural precursors in the adult subventricular zone and hippocampus. J Neurosci Res. 2013; 91: 642-659.

16. Lee J, Kemper JK. Controlling SIRT1 expression by microRNAs in health and metabolic disease. Aging (Albany NY). 2010; 2: 527-534.

17. Khojah SM. The Relationship between the Sirtuins and Slowing the Aging. J Biochem Tech. 2019; 10: 51-55.

18. Freitas M, Rodrigues AR, Tomada N, Fonseca J, Magalhaes A, Gouveia AM, et al. Effects of Aging and Cardiovascular Disease Risk Factors on the Expression of Sirtuins in the Human Corpus Cavernosum. J Sex Med. 2015; 12: 2141-2152.

19. Alcendor RR, Gao S, Zhai P, Zablocki D, Holle E, Yu X, et al. Sirt1 regulates aging and resistance to oxidative stress in the heart. Circ Res. 2007; 100: 1512-1521.

20. Kilic U, Gok O, Erenberk U, Dundaroz MR, Torun E, Kucukardali Y, et al. A remarkable age-related increase in SIRT1 protein expression against oxidative stress in elderly: SIRT1 gene variants and longevity in human. PLoS One. 2015; 10: e0117954.

21. Di Emidio G, Falone S, Vitti M, D'Alessandro AM, Vento M, Di Pietro C, et al. SIRT1 signalling protects mouse oocytes against oxidative stress and is deregulated during aging. Hum Reprod. 2014; 29: 2006-2017.

22. Mun J, Jung J, Park C. Effects of cerebral hypoperfusion on the cerebral white matter: a metaanalysis. Acta Neurobiol Exp (Wars). 2021; 81: 295-306.

23. Wojciak G, Szymura J, Szygula Z, Gradek J, Wiecek M. The Effect of Repeated Whole-Body Cryotherapy on Sirt1 and Sirt3 Concentrations and Oxidative Status in Older and Young Men Performing Different Levels of Physical Activity. Antioxidants (Basel). 2020; 10: 10.3390/antiox10010037.

24. Caldeira CA, Santos MA, Araujo GR, Lara RC, Franco FN, Chaves MM. Resveratrol: Change of SIRT 1 and AMPK signaling pattern during the aging process. Exp Gerontol. 2021; 146: 111226.

25. Opstad TB, Kalstad AA, Holte KB, Berg TJ, Solheim S, Arnesen H, et al. Shorter Leukocyte Telomere Lengths in Healthy Relatives of Patients with Coronary Heart Disease. Rejuvenation Res. 2020; 23: 324-332.

26. Wongchitrat P, Pakpian N, Kitidee K, Phopin K, Dharmasaroja PA, Govitrapong P. Alterations in the Expression of Amyloid Precursor Protein Cleaving Enzymes mRNA in Alzheimer Peripheral Blood. Curr Alzheimer Res. 2019; 16: 29-38.

27. Lee HJ, Yang SJ. Aging-Related Correlation between Serum Sirtuin 1 Activities and Basal Metabolic Rate in Women, but not in Men. Clin Nutr Res. 2017; 6: 18-26.

28. Zhong Y, Chen AF, Zhao J, Gu YJ, Fu GX. Serum levels of cathepsin D, sirtuin1, and endothelial nitric oxide synthase are correlatively reduced in elderly healthy people. Aging Clin Exp Res. 2016; 28: 641-645.

29. Yang Y, Tian T, Wang Y, Li Z, Xing K, Tian G. SIRT6 protects vascular endothelial cells from angiotensin II-induced apoptosis and oxidative stress by promoting the activation of Nrf2/ARE signaling. Eur J Pharmacol. 2019; 859: 172516.

30. Kumar R, Mohan N, Upadhyay AD, Singh AP, Sahu V, Dwivedi S, et al. Identification of serum sirtuins as novel noninvasive protein markers for frailty. Aging Cell. 2014; 13: 975-980.

31. Kumar R, Chaterjee P, Sharma PK, Singh AK, Gupta A, Gill K, et al. Sirtuin1: a promising serum protein marker for early detection of Alzheimer's disease. PLoS One. 2013; 8: e61560.

32. Pukhalskaia AE, Dyatlova AS, Linkova NS, Kozlov KL, Kvetnaia TV, Koroleva MV, et al. Sirtuins as Possible Predictors of Aging and Alzheimer's Disease Development: Verification in the Hippocampus and Saliva. Bull Exp Biol Med. 2020; 169: 821-824.

33. Spirichev AA, Moiseev KY, Masliukov PM. Sirtuin 1 Expression in the Rat Ventromedial and Dorsomedial Hypothalamic Nuclei during Ageing. Bull Exp Biol Med. 2020; 169: 698-700.

34. Singh S, Singh AK, Garg G, Rizvi SI. Fisetin as a caloric restriction mimetic protects rat brain against aging induced oxidative stress, apoptosis and neurodegeneration. Life Sci. 2018; 193: 171-179.

35. Wong DW, Soga T, Parhar IS. Aging and chronic administration of serotonin-selective reuptake inhibitor citalopram upregulate Sirt4 gene expression in the preoptic area of male mice. Front Genet. 2015; 6: 281.

36. Carbone A, Linkova N, Polyakova V, Mironova E, Hashimova U, Gadzhiev A, et al. Melatonin and Sirtuins in Buccal Epithelium: Potential Biomarkers of Aging and Age-Related Pathologies. Int J Mol Sci. 2020; 21: 10.3390/ijms21218134.

37. Liao FX, Huang F, Ma WG, Qin KP, Xu PF, Wu YF, et al. The New Role of Sirtuin1 in Human Osteoarthritis Chondrocytes by Regulating Autophagy. Cartilage. 2021; 13: 1237S-1248S.

38. Massudi H, Grant R, Braidy N, Guest J, Farnsworth B, Guillemin GJ. Age-associated changes in oxidative stress and NAD+ metabolism in human tissue. PLoS One. 2012; 7: e42357.

39. Sanchez-Roman I, Gomez A, Perez I, Sanchez C, Suarez H, Naudi A, et al. Effects of aging and methionine restriction applied at old age on ROS generation and oxidative damage in rat liver mitochondria. Biogerontology. 2012; 13: 399-411.

40. Donato AJ, Magerko KA, Lawson BR, Durrant JR, Lesniewski LA, Seals DR. SIRT-1 and vascular endothelial dysfunction with ageing in mice and humans. J Physiol. 2011; 589: 4545-4554.

41. Machida S, Booth FW. Increased nuclear proteins in muscle satellite cells in aged animals as compared to young growing animals. Exp Gerontol. 2004; 39: 1521-1525.

42. Ferrara N, Rinaldi B, Corbi G, Conti V, Stiuso P, Boccuti S, et al. Exercise training promotes SIRT1 activity in aged rats. Rejuvenation Res. 2008; 11: 139-150.

43. Zeng Y, Yang K. Sirtuin 1 participates in the process of age-related retinal degeneration. Biochem Biophys Res Commun. 2011; 468: 167-172.

44. Huang CC, Wang T, Tung YT, Lin WT. Effect of Exercise Training on

Skeletal Muscle SIRT1 and PGC-1alpha Expression Levels in Rats of Different Age. Int J Med Sci. 2016; 13: 260-270.

45. Xiu C, Jiang J, Song R. Expression of miR-34a in cataract rats and its related mechanism. Exp Ther Med. 2020; 19: 1051-1057.

46. Kanfi Y, Naiman S, Amir G, Peshti V, Zinman G, Nahum L, et al. The sirtuin SIRT6 regulates lifespan in male mice. Nature. 2012; 483: 218-221.

47. Stamatovic SM, Martinez-Revollar G, Hu A, Choi J, Keep RF, Andjelkovic AV. Decline in Sirtuin-1 expression and activity plays a critical role in blood-brain barrier permeability in aging. Neurobiol Dis. 2019; 126: 105-116.

48. Li X, Khanna A, Li N, Wang E. Circulatory miR34a as an RNAbased, noninvasive biomarker for brain aging. Aging (Albany NY). 2011; 3: 985-1002.

49. Ito T, Yagi S, Yamakuchi M. MicroRNA-34a regulation of endothelial senescence. Biochem Biophys Res Commun. 2010; 398: 735-740.

50. Kou X, Liu X, Chen X, Li J, Yang X, Fan J, et al. Ampelopsin attenuates brain aging of D-gal-induced rats through miR-34a-mediated SIRT1/mTOR signal pathway. Oncotarget. 2016; 7: 74484-74495.

51. Koltai E, Szabo Z, Atalay M, Boldogh I, Naito H, Goto S, et al. Exercise alters SIRT1, SIRT6, NAD and NAMPT levels in skeletal muscle of aged rats. Mech Ageing Dev. 2010; 131: 21-28.

52. Michishita E, McCord RA, Berber E, Kioi M, Padilla-Nash H, Damian M, et al. SIRT6 is a histone H3 lysine 9 deacetylase that modulates telomeric chromatin. Nature. 2008; 452: 492-496.

53. Pan H, Guan D, Liu X, Li J, Wang L, Wu J, et al. SIRT6 safeguards human mesenchymal stem cells from oxidative stress by coactivating NRF2. Cell Res. 2016; 26: 190-205.

54. Lee OH, Woo YM, Moon S, Lee J, Park H, Jang H, et al. Sirtuin 6 deficiency induces endothelial cell senescence via downregulation of forkhead box M1 expression. Aging (Albany NY). 2020; 12: 20946-20967.

55. Ravi V, Jain A, Khan D, Ahamed F, Mishra S, Giri M, et al. SIRT6 transcriptionally regulates global protein synthesis through transcription factor Sp1 independent of its deacetylase activity. Nucleic Acids Res. 2019; 47: 9115-9131.

56. Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ. 2011; 343: d4002.