Sirtuin 2

Sirtuins are NAD(+)-dependent deacetylases that regulate numerous cellular processes including aging, DNA repair, cell cycle, metabolism, and survival under stress conditions. The roles of sirtuin family members are widely studied in carcinogenesis.

Increasing evidence suggests the important role of sirtuin 2 (SIRT2) in the pathology of Parkinson's disease (PD). However, the association between potential functional polymorphisms in the SIRT2 gene and PD still needs to be identified. Exploring the molecular mechanism underlying this potential association could also provide novel insights into the pathogenesis of this disorder.

Bioinformatics analysis and screening were first performed to find potential microRNAs (miRNAs) that could target the SIRT2 gene, and molecular biology experiments were carried out to further identify the regulation between miRNA and SIRT2 and characterize the pivotal role of miRNA in PD models. Moreover, a clinical case-control study was performed with 304 PD patients and 312 healthy controls from the Chinese Han population to identify the possible association of single nucleotide polymorphisms (SNPs) within the miRNA binding sites of SIRT2 with the risk of PD.

Here, we demonstrate that miR-486-3p binds to the 3' UTR of SIRT2 and influences the translation of SIRT2. MiR-486-3p mimics can decrease the level of SIRT2 and reduce a-synuclein (α-syn)-induced aggregation and toxicity, which may contribute to the progression of PD. Interestingly, we find that a SNP, rs2241703, may disrupt miR-486-3p binding sites in the 3' UTR of SIRT2, subsequently influencing the translation of SIRT2. Through the clinical case-control study, we further verify that rs2241703 is associated with PD risk in the Chinese Han population.

The present study confirms that the rs2241703 polymorphism in the SIRT2 gene is associated with PD in the Chinese Han population, provides the potential mechanism of the susceptibility locus in determining PD risk and reveals a potential target of miRNA for the treatment and prevention of PD [1)].

Previous studies have reported an association between human sirtuins' single-nucleotide polymorphisms (SNPs) and Alzheimer's disease (AD) susceptibility in the apolipoprotein E (APOE) ε4-negative population, although the findings are inconsistent. To obtain a more precise estimation of this relationship, we conducted a meta-analysis to assess the association between the rs10410544 C/T polymorphism of SIRT2 and the risk of AD with APOE ε4 status. We searched all relevant PubMed publications and included three studies in our meta-analysis involving a total of 1,794 patients and 2,054 control subjects. Odds ratios (ORs) with 95% confidence intervals (CIs) were employed to evaluate the association of the SIRT2 SNP with AD susceptibility, and we analyzed the extracted data stratified by the APOE ε4-carrying status. Overall, the results show that the SIRT2 SNP is associated with human AD risk in the comparison models (T vs. C: OR 1.140, 95% CI 1.034-1.258; TC vs. CC: OR 1.178, 95% CI 1.019-1.361; TT + TC vs. CC: OR 1.197, 95% CI 1.043-1.373). In the stratified analyses, the European population had a significantly increased risk of AD (T vs. C: OR 1.110, 95% CI 1.002-1.229), and we also observed a significant association in the APOE ε4-negative population (T vs. C: OR 1.165, 95% CI 1.025-1.324; TT + TC vs. CC: OR 1.222, 95% CI 1.022-1.461). This meta-analysis indicates that the presence of the SIRT2 SNP with APOE ε4-negative status contributes to the development of AD in humans Epidemiological studies of larger sample sizes are warranted to confirm this hypothesis [2)].

Their roles in glioma remain unclear.

Li et al., reportedthat Sir2 was under expressed in human glioma tissues and cell lines. They found that Sirt2 overexpression decreased cell proliferation and colony formation capacity. In addition, Sirt2 overexpression induced cellular apoptosis via up-regulating cleaved caspase 3 and Bax, and down-regulating anti-apoptotic protein Bcl-2. Sirt2 knockdown obtained opposing results. We showed that Sirt2 overexpression inhibited miR-21 expression, and Sirt2 was not sufficient to reduce cell proliferation and colony formation as well as to induce apoptosis when miR-21 was knocked down in glioma cells. Mechanically, they demonstrated that Sirt2 deacetylated p65 at K310 and blocked p65 binding to the promoter region of miR-21, thus regressing the transcription of miR-21. In summary, Sirt2 is critical in human glioma via NF-κB-miR-21 pathway and Sirt2 activator may serve as candidate drug for glioma therapy [3)]

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