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Inhibition of SIRT1 Transcription in Resveratrol-differentiated Medulloblastoma Cells

Jing-Xin Ma, Hong Li, Xiao-Xin Cheng, Mo-Li Wu, Li-Jun Yu, Qing-You Kong, Ming Liu, Jia Liu

Liaoning Laboratory of Cancer Genetics and Epigenetics and Department of Cell Biology, Dalian Medical University, Dalian 116044, China

Corresponding author: Professor Jia Liu, Liaoning Laboratory of Cancer Genetics & Epigenetics and Department of Cell Biology, Dalian Medical University, Dalian 116044, China.

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ABSTRACT:

Backgrounds: Medulloblastoma (MB) is the commonest brain malignancy in childhood with poor prognosis, because of its rapid aggressive growth and frequent occurrence. The current chemotherapeutic regimens for medulloblastoma patients involve a combination of lomustine, cisplatin, carboplatin, vincristine or cyclophosphamide, which have distinct short- and long-term side-effects. It is therefore in urgent need to explore safer and more effective adjuvant approach(s). Resveratrol, a polyphenol rich in numerous plants, has multiple biological activities including anticancer effects. Our previous data confirmed that resveratrol inhibited proliferation and induced differentiation and apoptosis of medulloblastoma cells. SIRT1 is a deacetylase of class III HDACs and the supposed molecular effecter of resveratrol. SIRT1 involves in aging prevention and cancer formation in a cell-context specific manner. Nevertheless, the datum concerning the role(s) of SIRT1 in formation and prognosis of medulloblastoma is still missing.

Objective: The present study aimed to address the expression patterna of SIRT1 in medulloblastoma tissues and non-cancerous counterparts and to explore whether resveratrol exerts its anti-medulloblastoma effects via regulating SIRT1 expression and bioactivity.

Methods: The expression of SIRT1 in medulloblastoma and non-cancerous counterparts was elucidated by immunohistochemical ataining (IHC). To clarify the function of SIRT1 in medulloblastomas, SIRT1 expression in UW228-3 medulloblastoma cells were suppressed by

RNA interference (RNAi). The influence of resveratrol in SIRT1 expressions in UW228-3 cells was analyzed by reverse transcription-polymerase chain reaction (RT-PCR), immunocytochemistry (ICC) and Western blotting (WB). The catalytic activity of deacetylase SIRT1 was examined by measuring the acetylation of the main substrate p53.

Results: IHC staining revealed that SIRT1 was expressed in 64.17% of MB tissues, which was higher than that in noncancerous cerebellum tissues (14.29%). The frequencies of SIRT1 expression in the nodular MB (22.22%) with better prognosis is lower than that in anaplastic MB (79.07%) and classic MB (60.29 %; $P<0.05$). The proliferation of UW228-3 cells was remarkably suppressed after being transfected with SIRT1 siRNA, accompanied with extensive cell death. The results of RT-PCR and WB showed that after 48 hours 100□M resveratrol treatment, SIRT1 expression in UW228-3 cells was down-regulated at both transcriptional and translational levels. However, resveratrol has no effect on the deacetylase activity of SIRT1.

Conclusion: The above findings suggested that SIRT1 expression is corrected with the formation and prognosis of human MB. Resveratrol influences SIRT1 functioning in human MB cells through inhibiting SIRT1 expression rather than modulating its acetylation activity.

Keywords: resveratrol, SIRT1, RNA interference, deacetylase, medulloblastoma