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Badr-Eddine Allal1, Clara Quintas2, Abdelkader Bounaama1, Paula Fresco2, Jorge Gonçalves2, Bahia Djerdjouri1

1Laboratory of Cellular And Molecular Biology, University of Sciences And Technology Houari Boumediene
2Laboratory of Pharmacology, Faculty of Pharmacy, University of Porto

In Silico and In Vivo Investigations of SIRTUIN4: Implications for Tumor Suppression and Chemotherapy Resistance in Colorectal Cancer

Abstract:

Background: Identification of tumor suppressors in colorectal cancer (CRC) is crucial for developing effective treatments. SIRTUIN4 (SIRT4), a member of the sirtuin family of NAD+-dependent enzymes, has emerged as a potential tumor suppressor in various cancers. This study aims to investigate the involvement of SIRT4 colon adenocarcinoma (COAD and its potential implications for therapeutic strategies.

Methods: We first used a comprehensive bioinformatic approaches utilizing webtools based on The Cancer Genome Atlas (TCGA) database to analyze the mRNA expression and methylation profile of SIRT4 in COAD. Additionally, we examined the association of SIRT4 with drug resistance using the Genomics of Drug Sensitivity in Cancer (GDSC) database. Then, we conducted protein-protein interaction (PPI) analysis to identify potential SIRT4 targets. Furthermore, we validated the mRNA expression of SIRT4 in a translational model of 1,2-dimethylhydrazine (DMH)-induced COAD in mice administration.

Results: Bioinformatic analyzes revealed a hypermethylation of SIRT4 gene and its promoter, leading to a significant downregulation of SIRT4 mRNA in COAD patients. GDSC database evidenced that SIRT4 was associated with resistance to serine/threonine kinase inhibitors and histone deacetylase 6 (HDAC6) inhibitors. PPI analysis identified glutamate dehydrogenase 1 (GDH1), a key glutaminolysis enzyme in COAD, as a target inhibited by SIRT4. In vivo, DMH administration resulted in COAD development and confirmed the decreased SIRT4 expression. Although GDH1 mRNA levels remained unaffected, its biochemical activity was significantly reduced in DMH-treated mice. Conclusion: Altogether, our results suggest that SIRT4 functions as a tumor suppressor in COAD by inhibiting GDH1, an oncogene that plays controls glutamine metabolism in COAD. Furthermore, the association of SIRT4 with chemotherapy resistance highlights its potential as a therapeutic target.

Keywords: SIRT4, GDH1, 1,2-Dimethylhydrazine, HDAC6, TCGA

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