論 文 要 旨

EHHADH contributes to cisplatin resistance through regulation by tumor-suppressive microRNAs in bladder cancer

（シスプラチン耐性膀胱癌における、癌抑制型 microRNA を介した、*EHHADH* の役割）

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【Abstract】

Background: Cisplatin-based chemotherapy is recommended as the primary treatment for advanced bladder cancer (BC) with unresectable or metastatic disease. However, the benefits are limited due to the acquisition of drug resistance. The mechanisms of resistance remain unclear. Although there are some reports that some molecules are associated with cisplatin resistance in advanced BC, those reports have not been fully investigated. Therefore, we undertook a new search for cisplatin resistance-related genes targeted by tumor suppressive microRNAs as well as genes that were downregulated in cisplatin-resistant BC cells and clinical BC tissues.

Methods: First, we established cisplatin-resistant BOY and T24 BC cell lines (CDDP-R-BOY, CDDP-R-T24). Then, Next Generation Sequence analysis was performed with parental and cisplatin-resistant cell lines to search for the microRNAs responsible for cisplatin resistance. We conducted gain-of-function analysis of microRNAs and their effects on cisplatin resistance, and we searched target genes comprehensively using Next Generation mRNA sequences.

Results: A total of 28 microRNAs were significantly downregulated in both CDDP-R-BOY and CDDP-R-T24. Among them, miR-486-5p, a tumor suppressor miRNA, was negatively correlated with the TNM classification of clinical BC samples in The Cancer Genome Atlas (TCGA) database. Transfection of miRNA-486-5p significantly inhibited cancer cell proliferation, migration, and invasion, and also improved the cells' resistance to cisplatin. Among the genes targeted by miRNA-486-5p, we focused on enoyl-CoA, hydratase/3-hydroxyacyl CoA dehydrogenase (EHHADH), which is involved in the degradation of fatty acids. EHHADH was directly regulated by miRNA-486-5p as determined by a dual-luciferase reporter assay. Loss-of-function study using EHHADH si-RNA showed significant inhibitions of cell proliferation, migration, invasion and the recovery of cisplatin sensitivity.

Conclusion: Identification of EHHADH as a target of miRNA-486-5p provides novel insights into the potential mechanisms of cisplatin resistance in BC.

(BMC cancer　2021 11;21(1):48)