IRAK1, A TARGET OF MIR-146B, REDUCES CELL AGGRESSIVENESS OF HUMAN PAPILLARY THYROID CARCINOMA

Chen-Kai Chou, Shun-Yu Chi, Cai-Hua Huang, Fong-Fu Chou, Chao-Cheng Huang, Rue-Tsuan Liu, Hong-Yo Kang

Division of Endocrinology and Metabolism, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taiwan, Graduate Institute of Clinical Medical Sciences, Chang Gung University, Taiwan, Departments of Surgery, Pathology Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taiwan,

Objective: MicroRNA (miR)-146b is overexpressed in papillary thyroid carcinoma (PTC) and is associated with extrathyroidal invasion, advanced tumor stage, and poor prognosis. However, the underlying mechanism of miR-146b in relation to its oncogenic behavior in PTC and its putative targets remain unknown. The purpose of this study was to investigate interleukin-1 receptor-associated kinase 1 (IRAK1) as the potential miR-146b target gene and its involvement in PTC.

Design: We used genome-wide microarray, computational analysis and 3′ UTR reporter gene assays to identify IRAK1 as a miR-146b target gene. In vitro gain/loss-of-function experiments were further performed to determine the effects of IRAK1 on proliferation, colony formation, and wound-healing in PTC cancer cell lines. Expression levels of miR-146b and IRAK1 of 50 cases of PTC and its adjacent normal thyroid specimens were assessed via quantitative real-time polymerase chain reaction.

Results: Microarray expression profile revealed that the mRNA level of IRAK1 gene was downregulated by miR-146b. The 3′ UTR of IRAK1 mRNA was found to be a molecular target of miR-146b posttranscriptional repression in BCPAP cells by reporter gene assays. MiR-146b promoted the migration and proliferation of PTC cells by downregulating IRAK1 expression, whereas restoration of IRAK1 expression reversed this effect. In addition, the expression of IRAK1 mRNA was significantly lower in PTC clinical tissue samples than normal adjacent thyroid specimens and showed a strong inverse correlation with the expression of miR-146b in PTC specimens.

Conclusion: Our results demonstrated that IRAK1 is a direct target of miR-146b and has functional roles to inhibit various aggressive PTC cell activities. In conjunction with current therapeutic regimens, targeting the miR-146b-IRAK1 axis may provide a potential approach for PTC management.