Role of miR-338-5p as a novel modulator of chemoresistance in esophageal cancer

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INTRODUCTION: Multimodal treatment incorporating surgical resection and the use of chemotherapeutic drugs is commonly used in the management of esophageal cancer. However, resistance to chemotherapy drugs may contribute to poor treatment outcome and cancer recurrence. Increasing evidence suggests that miRNAs regulate the sensitivity of cancer to chemotherapeutic drugs. 5-Fluorouracil (5-FU) is an antimetabolite agent commonly used to treat esophageal cancer.

MATERIAL AND METHOD: We have established 5-FU-resistant (FR) esophageal squamous cell carcinoma (ESCC) cell lines as cell models to study the mechanisms of chemoresistance. These FR cell lines overexpress thymidylate synthase, which is generally regarded as a marker of 5-FU resistance.

RESULTS AND DISCUSSION: We found that miR-338-5p was downregulated whereas Id1, which was one of its predicted targets according to target prediction algorithms, was upregulated in the FR cells. Luciferase reporter assay confirmed that miR-338-5p could directly bind to the 3’ untranslated region (UTR) of Id1. Overexpression of miR-338-5p downregulated endogenous Id1 protein level in esophageal cancer cell lines, whereas knockdown of miR-338-5p produced the opposite effect. The inhibitory effect of miR-338-5p on Id1 expression was further confirmed using Tet-on ESCC cell lines inducible for miR-338-5p expression. Flow cytometry and Western blotting were performed to study the effects of miR-338-5p overexpression and inhibition on 5-FU-induced apoptosis. The results showed that miR-338-5p overexpression restored sensitivity of the FR cells to 5-FU treatment both in vitro and in vivo, and that knockdown of miR-338-5p induced 5-FU resistance in chemosensitive esophageal cells. These effects were abolished by expression of Id1 and shId1, respectively.

CONCLUSION: Taken together, our data suggest that miR-338-5p can modulate the chemosensitivity of ESCC cells by regulating Id1. Since previous studies showed that Id1 is frequently upregulated in ESCC and is a marker for unfavorable prognosis, miR-338-5p and its suppressive effect on Id1 may be exploited to develop novel therapies for treatment of esophageal cancer.