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MiR-199a-5p and miR-375 affect colon cancer cell sensitivity to cetuximab by targeting PHLPP1.

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Abstract

OBJECTIVES:

We aimed to analyze the differentially-expressed miRNAs in colon cancer cells in order to identify novel potential biomarkers involved in cancer cell resistance.

DESIGN AND METHODS:

We investigated the miRNA expression profile of GEO human colon carcinoma cells, sensitive to the EGFR inhibitor Cetuximab (CTX) and their CTX-resistant counterpart (GEO CR) by using a miRNA chip.

RESULTS:

We found 27 upregulated and 10 downregulated miRNAs in GEO CR compared with GEO cells with a fold change ≥ 2. Among the upregulated miRNAs, we focused on miR-199a-5p and miR-375. We report that their enforced expression promotes CTX resistance, whereas their silencing sensitizes to the same drug. The ability of miR-199a-5p and miR-375 to target PHLPP1 (PH domain and leucine-rich repeat protein phosphatase 1), a tumor suppressor that negatively regulates the AKT pathway, accounts, at least in part, for their drug-resistance activity. Indeed, restoration of PHLPP1 increases sensitivity of the GEO cells to CTX and reverts the resistance-promoting effect of miR-199a-5p and miR-375.

CONCLUSION:

This study proposes miR-199a-5p and miR-375 as contributors to CTX resistance in colon cancer and suggests a novel approach based on miRNAs as tools for the therapy of this tumor.

KEYWORDS:

colon cancer; drug resistance; miR-199a-5p; miR-375

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