Production, structure, and function analyses of a recombinant miR-1291 agent

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Abstract ID 25922 Poster Board 378

MicoRNAs are a superfamily of small, regulatory noncoding RNAs that play essential roles in almost all cellular processes, including drug and nutrient transport and metabolism as well as disease progression. Previous studies have revealed that microRNA-1291-5p (miR-1291) is able to sensitize pancreatic cancer (PC) cells to chemotherapies via regulating drug efflux transporter ABCC1/ABCG1 and glucose uptake transporter SLC2A1/GLUT1. Our recent studies have also shown that miR-1291 acts as a tumor suppressor, whereas it is downregulated in PC patient tissues and cell lines. In this study, we aimed to produce and characterize a recombinant miR-1291 agent to further understand miR-1291 functions and explore new therapy. Human seryl-tRNA was fused to human pre-miR-1291 to offer recombinant miR-1291 (BioRNA/miR-1291). The BioRNA/miR-1291 showed high-level expression in bacteria fermentation and was subsequently purified to high homogeneity (> 97%). While computational modeling indicated a possible rigid structure, cryogenic electron microscopy (cryo-EM) study revealed the presence of highly flexible structures for BioRNA/miRNA-1291. Further studies demonstrated that miR-1291-5p was selectively released from BioRNA/miR-1291 in PC cells to alter cell transcriptome. Moreover, PNPO, a key enzyme in vitamin B6 biosynthesis, was identified and validated as a new target for miR-1291-5p, which led to the control of VB6 homeostasis in human PC cells. In addition, the effectiveness of BioRNA/miR-1291 in improving the pharmacodynamics of another metabolic modulator 5-FU was delineated in both PC patient-derived organoid and xenograft mouse models. These results demonstrate a critical role for miR-1291 in the regulation of nutrient metabolism and provide insights into developing new therapeutic strategies.

This study was supported by the National Institute of General Medical Sciences (grant No. R35GM140835) and the National Cancer Institute (R01CA253230), National Institutes of Health.