Published OnlineFirst July 23, 2013; DOI: 10.1158/1078-0432.CCR-13-1899

Clinical Cancer Research

Letter to the Editor

Serum miR-1290 as a Marker of Pancreatic Cancer—Response

Ang Li[1], Jun Yu[1], Haeryoung Kim[1], Christopher L. Wolfgang[2], Marcia Irene Canto[3,4], Ralph H. Hruban[1,4], and Michael Goggins[1,3,4]

The authors thank Frampton and colleagues for their interest in our study. They commented on our use of miR-16, stating that because studies have reported that red blood cells are a major source of miR-16 and serum levels are elevated in hemolyzed blood samples, there is debate about whether it is a suitable endogenous control for serum micro RNAs (miRNA). We agree that hemolyzed samples would confound serum miRNA levels, but other characteristics of miR-16 make it a useful and widely used endogenous control for serum miRNA analysis. We did not use hemolyzed samples in our study.

They also recommend that miR-1290 and miR-486-3p be validated in independent cohorts, as only miR-1290, not miR-486-3p was evaluated by both quantitative reverse transcriptase PCR (qRT-PCR) and locked nucleic acid (LNA)-Fluorescent *in situ* hybridization (FISH). This comment appears to be commenting on the tissue expression of these miRNAs, as we did have pilot and validation sample sets for the serum miRNA marker analysis. They describe pancreatic tissue profiles of these 2 miRNAs in the gene expression omnibus (GEO) repository. In this analysis they find pancreatic cancer tissues have higher levels of miR-1290, but not miR-486-3p, relative to pancreatitis and healthy control pancreatic tissues, which they say indicates that the source of this miR-486-3p is unlikely to be derived from tumor cells. Although this analysis is a useful preliminary data, the samples used seem to be bulk pancreatic tissues and it is difficult to make firm conclusions of gene expression using bulk pancreatic tissues. To determine whether pancreatic cancer cells were a source of overexpression, we examined the tissue expression of 11 miRNAs we found to be elevated in serum of patients with pancreatic cancer by using laser capture microdissection to obtain pure samples. From this analysis, we found that miR-1290 (and 8 of 9 other miRNAs) was significantly elevated in the microdissected primary pancreatic ductal adenocarcinoma samples compared with normal pancreatic duct samples. We did not conduct FISH or qRT-PCR analysis of miR-486-3p in this study because it did not have promising diagnostic characteristics. However, we did previously confirm by miRNA array analysis and qRT-PCR that miR-486-3p was significantly elevated in PanIN-3 samples compared with normal pancreatic duct samples (1). We are not surprised that miR-486-3p levels were not higher in the bulk pancreatic tumor samples. Typically bulk primary pancreatic cancer tissues contain less than 50% cancer cells and are rich in stromal fibroblasts and immune cells. In contrast, approximately 90% of normal pancreas cells are acinar cells and the remaining are mostly ductal and islet cells as well as fibroblasts, immune cells, and adipocytes. Pancreatitis tissues are highly variable in their cellular composition. Differences in the proportions of cell types in bulk tissues can manifest as differences in marker expression between pancreatic cancer, pancreatitis, and normal pancreata even when no difference in expression exists between pancreatic cancer cells and duct cells. Bulk tissue comparisons can also obscure true differences in expression between cancer cells and normal duct cells.

We excluded patients with obstructive jaundice from our miRNA array analysis so as to avoid confounding effects of jaundice on serum miRNA levels. Understanding how serum miR-1290 behaves in the setting of jaundice would be interesting but jaundice is likely to affect the behavior of many circulating markers, which is why caution is needed when using such markers in the setting of jaundice.

We did report in the study that none of the other 16 miRNAs examined had prognostic significance as serum markers. This is not surprising because serum markers that are only modestly discriminating between cases and controls likely have other biologic factors influencing their serum levels minimizing their prognostic potential. As the primary goal of our study was to identify serum miRNAs with potential diagnostic use, our sample sizes were powered for diagnostic rather than for prognostic purposes and we recommended in the study that the prognostic significance of miR-1290 and miR-486-3p be confirmed with additional studies. Among patients who undergo surgical resection of their primary pancreatic cancer, there are multiple well-validated clinicopathologic factors associated with prognosis that should be accounted so as to identify markers with independent prognostic information and such analyses require a sufficiently large study population.

Authors' Affiliations: Departments of [1]Pathology, [2]Surgery, [3]Medicine, and [4]Oncology, The Sol Goldman Pancreatic Cancer Research Center, Johns Hopkins Medical Institutions, Johns Hopkins University, Baltimore, Maryland

Corresponding Author: Michael Goggins, The Johns Hopkins Medical Institutions, 342 CRB2, 1550 Orleans St., Baltimore, MD 21231. Phone: 1-410-955-3511; Fax: 1-410-614-0671; E-mail: mgoggins@jhmi.edu

doi: 10.1158/1078-0432.CCR-13-1899

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Grant Support

The work was supported by the National Cancer Institute Grants (CA62924, RC2148346; to M. Goggins), Susan Wojcicki and Dennis

Published OnlineFirst July 23, 2013; DOI: 10.1158/1078-0432.CCR-13-1899

Troper, The Alan Graff Memorial Foundation, and the Michael Rolfe Foundation.

Reference

1. Yu J, Li A, Hong SM, Hruban RH, Goggins M. MicroRNA alterations of pancreatic intraepithelial neoplasias. Clin Cancer Res 2012;18: 981–92.

Received July 10, 2013; accepted July 17, 2013; published OnlineFirst July 23, 2013.

Published OnlineFirst July 23, 2013; DOI: 10.1158/1078-0432.CCR-13-1899

Clinical Cancer Research

Serum miR-1290 as a Marker of Pancreatic Cancer—Response

Ang Li, Jun Yu, Haeryoung Kim, et al.

Clin Cancer Res 2013;19:5252-5253. Published OnlineFirst July 23, 2013.