

June 20th, 2017

To the Editor:

We thank you for the opportunity to revise the manuscript entitled “The Epigenetics of Gastroenteropancreatic Neuroendocrine Tumors: A Clinicopathologic Perspective”. We have made changes to the manuscript according to the reviewer’s suggestions.

Reviewer 1 Comments: “A list of abbreviations would be helpful. Please check the manuscript once more in order to eliminate some minor linguistic/grammatical problems.”

Response to Reviewer 1: A list of abbreviations has been compiled and will be submitted as supplementary Table 1 as below. We are also including a second supplementary table reviewing the effect of individual microRNA’s in neuroendocrine tumors (Supplementary table 2, below). Additionally, the grammatical errors mentioned by the reviewer have been corrected, including on lines 177, 178, 465.

Supplementary Table 1. List of abbreviations.

ALT	alternative lengthening of telomeres
AZA	5-azacytidine
ChIP	chromatin immunoprecipitation
DMR2	differentially methylated region 2
DNMT	DNA methyltransferase enzymes
FISH	fluorescence in situ hybridization
GEP-NET	Gastroenteropancreatic neuroendocrine tumor
GI-NET	Gastrointestinal neuroendocrine tumor
HDAC	histone acetyltransferases and deacetylases
LINE	long interspersed nucleotide elements
lncRNA	long noncoding RNA
miRNA	microRNA
mRNA	messenger RNA
NGS	Next-Generation Sequencing
PNET	Pancreatic neuroendocrine tumor
SB-NET	Small bowel neuroendocrine tumor
UTR	untranslated regions

Supplementary Table 2. Summary of MicroRNA's and their effect on tumor behavior.

miRNA	Effect	Tumor	Citation
Overexpression			
miR-7-5p	Marker of metastases	SB-NET	76
miR-19a	Marker of metastases	SB-NET	74
miR-21	Associated with Ki-67>2%, liver metastasis	PNET	72
miR-96	Marker of metastases	SB-NET	75, 76
miR-103	Marker of malignancy	PNET	72
miR-107	Marker of malignancy	PNET	72
miR-144	Marker of malignancy	PNET	79
miR-182	Marker of metastases	SB-NET	75, 76
miR-183	Marker of metastases	SB-NET	74, 75
miR-193b	Marker of malignancy	PNET	73
miR-196a	Marker of metastases, advanced stage	SB-NET, PNET	75, 76, 78
miR-200a	Marker of metastases	SB-NET	75, 76
miR-204	Specific for insulinoma, marker of metastases in SB-NET	Insulinoma, SB-NET	72, 76
miR-210	Marker of metastases	PNET	73
miR-375	Marker of metastases	SB-NET	76
miR-451	Marker of malignancy	PNET	79
miR-488	Marker of metastases	SB-NET	74
miR-642	Correlates with Ki-67 score	PNET	73
Underexpression			
miR-1	Marker of metastases	SB-NET	76
miR-10b	Marker of metastases	SB-NET	74
miR-31	Marker of metastases	SB-NET	75, 76
miR-129-5p	Marker of metastases	SB-NET	75, 76
miR-133a	Marker of metastases	SB-NET	74, 75, 76
miR-143-3p	Marker of metastases	SB-NET	76
miR-145	Marker of metastases	SB-NET	74, 76
miR-146	Marker of metastases	SB-NET	74
miR-155	Marker of malignancy	PNET	72
miR-215	Marker of metastases	SB-NET	75, 76
miR-222	Marker of metastases	SB-NET	74

Reviewer 2 Comments: “This is a very good overview of what is known about the genetics of NETs of the pancreas. Will be useful for the readership of the journal. Grade B: minor language polishing.”

Response to Reviewer 2: The manuscript has been reviewed for typographical and language errors and has been updated as listed in the Response to Reviewer 1 above.

Additionally, we would like to withdraw the funding disclosure from the title page (previously listed as “Supported in part by the Goldhirsch-Yellin Foundation”) as this study was internally funded without named contribution from this foundation.

Finally, we have submitted versions of the tables and figures in an editable format under Supplementary Material.

We thank you and the reviewers for the opportunity to enhance the quality of our manuscript.

Respectfully,

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