MicroRNA Signature as Novel Biomarkers in Small Intestine Neuroendocrine Tumors

Su-Chen Li[1]
Ahmed Essaghir[3]
Cécile Martijn[4]
Ricardo V. Lloyd[5]
JeanBaptiste Demoulin[3]
Kjell Öberg[2§]
Valeria Giandomenico[1§]

[1]Department of Medical Sciences, Endocrine Oncology

[2]Department of Medical Sciences, Uppsala University Hospital, Uppsala, Sweden

[3]Université Catholique de Louvain, de Duve Institute, Brussels, Belgium

[4]Department of Surgical Sciences, Anaesthesiology and Intensive Care, Uppsala University, Uppsala, Sweden

[5]Department of Pathology and Laboratory Medicine, University of Wisconsin, Madison Wisconsin, USA

[§]Science for Life Laboratory, Uppsala University, Uppsala, Sweden

Aims

Identification of exclusive microRNA (miR) profiles of small intestine neuroendocrine tumors (SI-NETs) at different stage of disease. Furthermore, to study potential miR targets, which may have a significant role in the development, prognosis and progression of SI-NETs.

Background

MicroRNAs are well known post-transcriptional regulators, which control cell proliferation, differentiation and apoptosis in a variety of cells. However, miR expression is not fully characterized in SI-NETs.

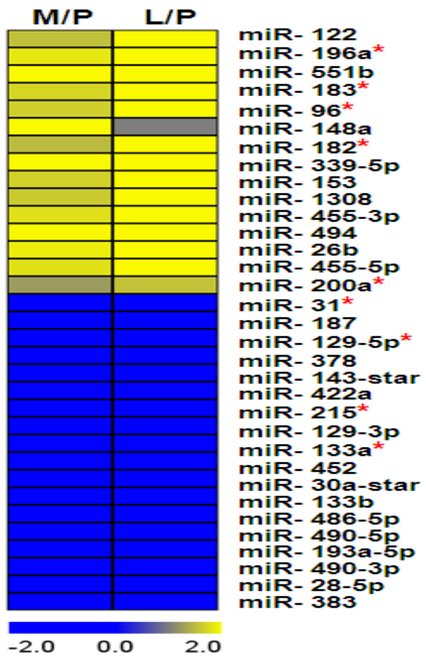

Figure 1. MiRs expression of SI-NET specimens. 33 differentially expressed miRs were detected both in mesentery metastateas (M) and liver metastateas (L) compared to primary tumors (P).

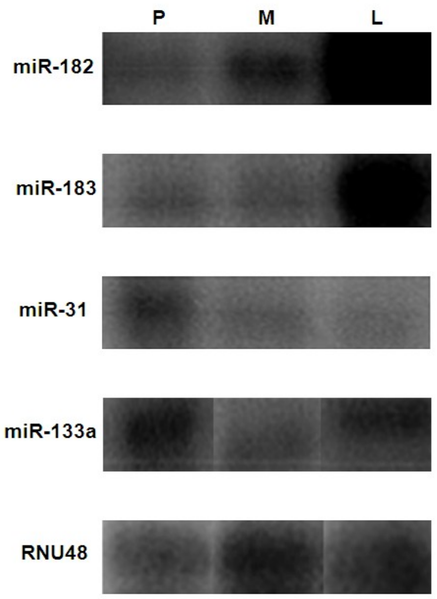

Figure 2. MiR-182, -183, -31 and -133a expression by Northern blot analysis. Total RNA from P, M and L was hybridized with ^{32}P radiolabeled RNA probes. RNU48 was used as internal control.

Material & Methods

Fifteen SI-NET specimens at different stage of malignancy (5 primary tumors, 5 mesentery metastases and 5 liver metastases) were included in this study. Total RNA was hybridized onto Affymetrix GeneChip® miR arrays for genome-wide profiling. Quantitative real time PCR (QRT-PCR) and Northern blot analyses on total RNA of the tumor specimens and microdissected SI-NET cells validated our *in silico* data.

Results & Conclusions

The expression of miR-96, -182, -183, -196a and -200a is significantly upregulated in microdissected SI-NET cells compared to microdissected normal enterochromaffin (EC) cells. MiR-31, -129-5p, -133a and -215 expression reveals significant downregulation in microdissected SI-NET cells compared to microdissected normal EC cells.

This genome-wide miRs expression analysis of SI-NETs at different stage of disease provides information about potential pivotal miRs. This may lead to further insights into tumorigenesis and progression mechanisms of these tumors.

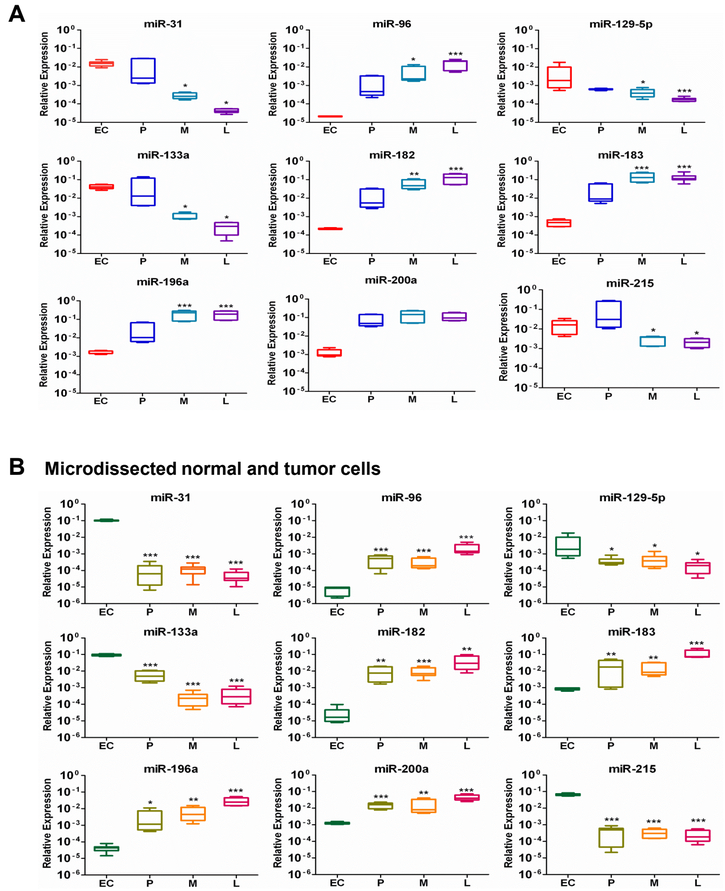

Figure 3. MiR-31, -96, -129-5p, -133a, -182, -183, -196a, -200a and -215 expression by QRT-PCR analysis. (A) Total RNA from frozen specimens (P, M and L) and microdissected normal enterochromaffin (EC) cells were used to verify miR arrays data. RNA from microdissected normal EC cells was used as a reference. (B) Total RNA from microdissected normal EC cells and SI-NET (P, M, and L) cells revealed specific miR expression levels in tumor cells. The internal control RNU48, from each individual sample set to 1 was used for normalization. Student's t-test calculated experimental significance.

* = $p < 0.05$, ** = $p < 0.01$ and *** = $p < 0.001$