Circulating microRNAs as predictors of response to therapy in melanoma

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Background & objectives

Patients suffering from metastatic melanoma can be treated with BRAF and MEK inhibitors (MAPKi) or immunotherapy with Checkpoint Inhibitors (ICIs). However, the efficacy of these treatments is limited in time by drug resistance. Therefore defining novel biomarkers to reliably identify patients who respond or develop resistance is an urgent medical need. In this context microRNAs (miRNAs) have emerged as promising candidates. This is what we have demonstrated in two recent studies, the first published (on MAPKi) and the second still unpublished (on ICIs).
Objective: To identify blood-based miRNA signatures able to predict response to 1) targeted therapies and 2) immunotherapies in metastatic melanoma.

Methods

1) Circulating miRNAs were extracted from the serum of 70 BRAF-mutated melanoma patients before the beginning of MAPKi therapy to perform qRT-PCR analyses for miR-204-5p, miR-199b-5p miR-579-3p, miR-9-5p miR-4443 and miR-4488 were performed. Data of circulating miRNAs were normalized using Global mean normalization and NormFinder model. 2) miRNA-seq profiling has been performed on serum samples from melanoma patients before starting ICIs as first line therapy. Receiver operating characteristics (ROC) and the Kaplan-Meier curves have been plotted to estimate the predictive values of circulating miRNAs.

Results

1) Results show that the circulating levels of the oncosuppressor miR-579-3p and of the oncomiR miR-4488 are able to predict progression free survival (PFS) but not overall survival (OS). The best predictive values of disease outcome have been obtained by the ratio of miR-4488 vs. miR-579-3p (miRatio). 2) A blood-based miRNA-seq profiling has been performed using samples from 48 melanoma patients before starting the anti-PD1 antibody, Nivolumab.

Patients have been divided into 24 responders (R) vs 24 non responders (NR) based on iRECIST criteria. Bioinformatics analyses unveiled a signature of 19 up- and 6- down regulated miRNAs significantly deregulated in NR vs R patients. ROC and Kaplan Meier curves confirm the capability of deregulated miRNAs to distinguish NR vs R patients with high sensitivity and specificity.

Conclusion

Altogether these data suggest that circulating miRNAs may represent suitable biomarkers to predict therapy response in melanoma to be further developed as companion diagnostics in the clinic.