Method for predicting the development of resistance to BRAF inhibiting drugs, alone or in combination with MEK inhibiting drugs, in an anti-tumour treatment

KEYWORDS

- ❑ microRNAs
- ❑ LIQUID BIOPSY
- ❑ DIAGNOSTIC
- ❑ RESISTANCE
- ❑ MELANOMA

AREA

- ❑ CHEMISTRY & BIOTECHNOLOGY

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Co-Ownership
Sapienza University of Rome 16%, Istituti Fisioterapici Ospitalieri 52%, Istituto Nazionale Tumori I.R.C.C.S. "Fondazione G. Pascale" 32%

Inventors
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Industrial & Commercial Reference
The subject matter disclosed in the claims appears to be industrially applicable in biotechnologies

Time to Market
The invention has been developed in blood samples derived from patients who developed resistance to therapy (TRL 4 – technology validated in lab)

Availability
Cession, Licensing, Research, Development, Experimentation e Collaboration.

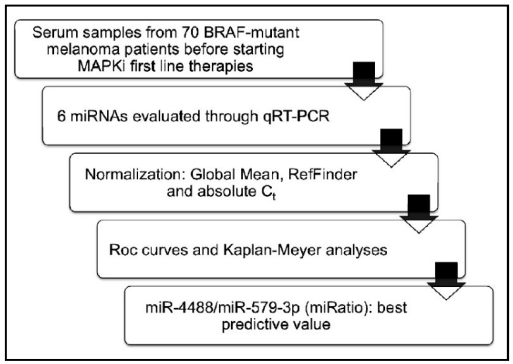

Fig. 1 Shows an on overview of the whole project. In detail, total RNAs were extracted from 70 serum samples of BRAF-mutated melanoma patients and then processed by qRT-PCR to assess the levels of 6 chosen miRNA candidates. Normalization of results have been performed through different methods and used to plot ROC and Kaplan-Meier curves. miR-4488/miR-579-3p (miRatio) showed the best predictive value.

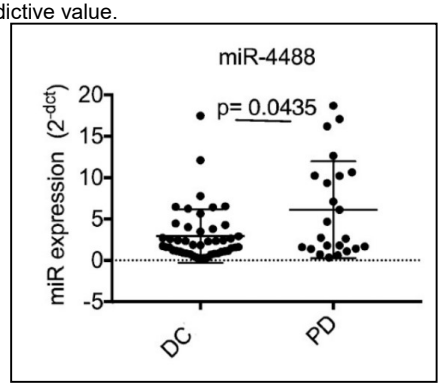

Fig. 2 Is a box plot graph showing that circulating levels (2^-dCt values calculated through GM normalization) of miR-4488 resulted significantly up-regulated in patients who did not benefit of treatments (PD) as compared to patients who benefited from MAPKi (DC).

Abstract
The present invention concerns a method for predicting the development of resistance to BRAF inhibiting drugs, alone or in combination with MEK inhibiting drugs (i.e. MAPK pathway inhibitors or simply MAPKi), in an anti-tumour treatment, wherein said method comprises measuring the expression of both microRNAs miR-579-3p and miR-4488 in a biological sample collected from a tumour patient before starting the anti-tumour treatment with the above mentioned MAPK pathway inhibiting drug and determining the ratio of expression of miR-4488 vs miR-579-3p.

Publications

❖ Fattore L, et al. MicroRNAs in melanoma development and resistance to target therapy. Oncotarget. 2017 Mar 28;8(13):22262-22278. doi: 10.18632/oncotarget.14763. pgg., Editor, Years.

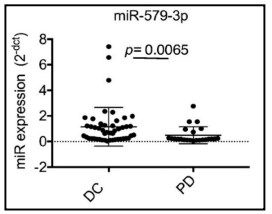

Fig. 3 E' is a box plot graph showing that circulating levels (2^-dCt values calculated through GM normalization) of miR-579-3p resulted significantly down-regulated in patients who did not benefit from treatment (PD) as compared to patients who benefited from MAPKi (DC).

Method for predicting the development of resistance to BRAF inhibiting drugs, alone or in combination with MEK inhibiting drugs, in an anti-tumour treatment

Technical Description

The present invention concerns a method for predicting the development of resistance to BRAF inhibiting drugs, alone or in combination with MEK inhibiting drugs (i.e., MAPK pathway inhibitors or simply MAPKi), in anti-tumour treatment. In particular, the present invention concerns a method for predicting the development of resistance to BRAF and/or MEK inhibiting drugs in anti-tumour treatment, wherein said method comprises measuring the expression levels of the two microRNAs miR-579-3p and miR-4488 in a biological sample collected from a cancer patient before starting the anti-tumour treatment with BRAF and/or MEK inhibitors.

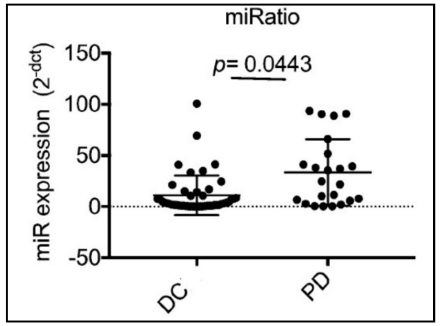

Fig. 4 Is a box plot graph showing that the relative ratio of the circulating levels of miR-4488 vs miR-579-3p (miRatio) resulted significantly up-regulated in patients who did not benefit of treatments (PD) as compared to patients who benefited from MAPKi (DC).

Technologies & Advantages

The present invention concerns the use of microRNAs as biomarkers for the in vitro diagnosis of the resistance of tumors to MAPK pathway According to an embodiment of the present invention, the method can comprise measuring the expression of different combinations of miRNAs in liquid biological samples such as blood, serum, plasma, urine.

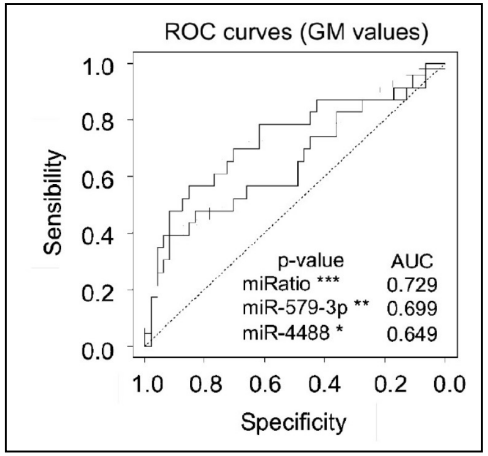

Fig. 5 Shows receiver operating characteristic (ROC) curves estimating the predictive value of miR-4488, miR-579-3p and miRatio (2^-dCt values calculated through GM normalization) as markers of drug resistance in basal serum samples.

Applications

The present invention relies on the unique characteristics of miRNAs that can be exploited for two different applications: diagnostic and therapeutic. As for the first one, these molecules can be easily extracted and tracked in human biological fluids, such as blood, and may represent future non invasive tools to predict disease evolution and drug resistance.

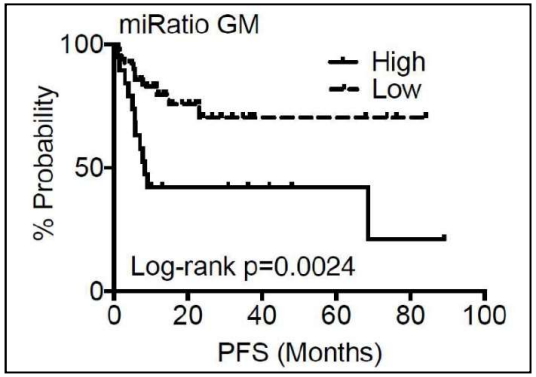

Fig. 6 Shows Kaplan-Meier curves showing that higher basal levels of miRatio (GM normalization) predict worst response to therapy in terms of PFS months (Log-rank p=0.0024).

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