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# Impact of BRAF kinase inhibitors on the miRNomes and transcriptomes of melanoma cells.

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### Abstract

#### BACKGROUND:

Melanoma is an aggressive skin cancer with increasing incidence worldwide. The development of BRAF kinase inhibitors as targeted treatments for patients with BRAF-mutant tumours contributed profoundly to an improved overall survival of patients with metastatic melanoma. Despite these promising results, the emergence of rapid resistance to targeted therapy remains a serious clinical issue.

#### METHODS:

To investigate the impact of BRAF inhibitors on miRNomes and transcriptomes, we used in vitro melanoma models consisting of BRAF inhibitor-sensitive and -resistant cell lines generated in our laboratory. Subsequently, microarray analyses were performed followed by RT-qPCR validations.

#### RESULTS:

Regarding miRNome and transcriptome changes, the long-term effects of BRAF inhibition differed in a cell line-specific manner with the two different BRAF inhibitors inducing comparable responses in three melanoma cell lines. Despite this heterogeneity, several miRNAs (e.g. miR-92a-1-5p, miR-708-5p) and genes (e.g. DOK5, PCSK2) were distinctly differentially expressed in drug-resistant versus -sensitive cell lines. Analyses of coexpressed miRNAs, as well as inversely correlated miRNA-mRNA pairs, revealed a low MITF/AXL ratio in two drug-resistant cell lines that might be regulated by miRNAs.

#### CONCLUSION:

Several genes and miRNAs were differentially regulated in the drug-resistant and -sensitive cell lines and might be considered as prognostic and/or diagnostic resistance biomarkers in melanoma drug resistance.

#### GENERAL SIGNIFICANCE:

Thus far, only little information is available on the significance and role of miRNAs with respect to kinase inhibitor treatments and emergence of drug resistance. In this study, promising miRNAs and genes were identified and associated to BRAF inhibitor-mediated resistance in melanoma. This article is part of a Special Issue entitled "Biochemistry of Synthetic Biology - Recent Developments" Guest Editor: Dr. Ilka Heinemann and Dr. Patrick O'Donoghue.

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#### KEYWORDS:

BRAF inhibitors; Drug resistance; Melanoma; Targeted therapy; miRNA

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