Mixed MiRNA and Serum-marker Classifier for Prediction of Immunotherapy Response in Liquid Biopsies of Melanoma Patients

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Background & objectives

Melanoma is a cutaneous tumor derived from melanocytes that poses a great challenge in clinical oncology due to its high propensity for metastasis and significant contribution to skin cancer-related mortalities, accounting for over 90% of such cases. The risk of melanoma development is closely associated with ultraviolet (UV) radiation exposure. Despite the advent of immune checkpoint inhibitor (ICI) therapy, including anti-PD1 and anti-CTLA4, the accurate assessment of treatment response remains a critical concern that necessitates the identification of reliable and stable biomarkers.

Methods

In this study, we investigated the utility of serum markers and plasma-derived miRNAs in developing a machine learning model that can accurately predict immunotherapy response in patients with advanced melanoma (Stage III or IV, AJCC classification). Serum markers were measured according to standard clinical procedures, while miRNA transcription was quantified using flowcytometric detection of 63 miRNAs selected based on a comprehensive review of the literature. Patients were categorized into responders and non-responders to immunotherapy based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria, and LASSO logistic regression was performed to predict therapy outcome using different sets of features. The area under the receiver operating characteristic (AUROC) curve was used as the performance metric, and to minimize overfitting, nested cross-validation was employed.

Results

Our findings revealed significant associations between the expression of five plasma-derived miRNAs (miR-132-3p, miR-137, miR-197, miR-214, and miR-514a-3p) and immunotherapy response. Additionally, the concentrations of serum markers, including lactate dehydrogenase (LDH), C-reactive protein (CRP), S100 protein, and eosinophils, were significantly altered

between responders and non-responders. Demographic parameters, such as age and prior anti-BRAF therapy, were also significantly associated with therapy outcome. The relaxed LASSO model was identified as the best-performing machine learning model out of six tested, with an AUROC of 0.851 on the whole dataset. Validation of the model in the outer loop of the nested cross-validation yielded an AUROC of 0.847. The identified model comprises a miRNA quartet, LDH, age, and prior anti-BRAF therapy, and displays high sensitivity and specificity in distinguishing responders from non-responders. The model presents potential candidates for further biomarker validation and investigation.

Conclusion

In conclusion, our study highlights the potential of plasma-derived miRNAs and serum markers as predictive biomarkers of immunotherapy response in advanced melanoma. The identified machine learning model can provide invaluable clinical guidance for treatment decisions and ultimately improve patient outcomes.