

Circulatory plasma proteomic biomarkers predict response to immunotherapy in melanoma patients and reveal biological insights into the tumor microenvironment

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Background & objectives

The majority of patients treated with immunotherapy do not have durable treatment responses. Therefore, there is an urgent need to identify early non-invasive biomarkers for treatment response.

Methods

In this study, we performed plasma proteomic analysis of >700 proteins at three timepoints on 174 metastatic melanoma patients treated with immune checkpoint blockade (ICB). We then expanded our analyses to >3000 proteins performed on a larger cohort of 250 patients for deeper exploration of baseline and early on-treatment predictive biomarkers for response to ICB treatment. As a result, we built a predictor of immunotherapy response that outperforms several tissue-based approaches.

Results

From the differentially expressed proteins between ICB responders (R) and non-responders (NR), we identified a co-regulated module of proteins associated with treatment resistance comprising IL-6, IL-8, MIA, LIF and GDF-15 enriched in certain NR patients. By analyzing single-cell RNA-sequencing data of tumor biopsies from 32 patients and bulk RNA-sequencing data from 70 patients, we determined the relative contribution of cells in the tumor to proteins in circulation, and associated plasma protein levels with tumor immune microenvironment (TME) phenotypes. The major TME subsets driving the expression of the non-response module proteins were tumor and myeloid cells. Amongst myeloid cells, a subset of tumor-associated macrophages (TAMs) with a suppressive phenotype were identified as potential key drivers of non-response, having the highest expression of all the proteins in the co-regulated NR module.

Conclusion

In summary, an integrated longitudinal analyses of circulatory plasma proteins, combined with TME transcriptomics, provides deeper insight into the biology of immunotherapy resistance, and demonstrates prognostic significance and utility of plasma proteomics in biomarker discovery for cancer immunotherapy.

