Immune and epigenetic characterization of cutaneous malignant melanoma tumors

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Abstract:

Cutaneous melanoma is an aggressive skin malignancy that arises in melanocytes and that when metastasize often result in poor prognosis. Recent advancement of targeted and immune checkpoint inhibitor treatments has resulted in prolonged survival for some patients; however, search for predictive biomarkers to select suitable patients is ongoing. Previous studies have emphasized the impact of the melanoma tumor immune microenvironment in prognosis. In light of these findings, this project aims to understand the role of the immune microenvironment in melanoma and what clinical and molecular factors that might influence the relationship. We also aim to explore DNA methylation changes in key melanoma processes and what tumor cell phenotypes are associated with such changes.

In study I we have used immune cell type associated DNA methylation based signatures on a large cohort of metastatic melanoma tumors. We found three distinct immune clusters for metastatic melanoma that significantly associates with patient survival. Additionally, these DNA methylation signatures showed prognostic implications in other solid tumor cohorts. In study II we are exploring other clinical parameters in relation to immune gene expression signatures. In particular, our analyses demonstrate a significant gender specific difference in expression of the immune cell type associated genes. Indeed, it is well established that there are survival differences between male and female metastatic melanoma patients.
suggesting tumor intrinsic differences that we will further investigate in study II. In
study III we have performed a comprehensive genomic analysis of metastatic
melanoma tumors obtained from patients enrolled in a clinical trial testing the clinical
efficacy of adoptive cell transfer therapy. Our analyses revealed that high tumor
mutational burden, putative neoantigen load and high expression of MHC I antigen
presentation genes associate with clinical benefit and might serve as future
biomarkers for patient selection. Finally, in study IV we are analyzing the cell
phenotypic effects of promoter hypermethylation of melanocyte lineage specific
genes. Preliminary data shows a strong correlation between hypermethylation and
decreased mRNA levels in tumors and cell lines as well as distinct melanoma
phenotypes in cells harboring promoter methylation of MITF and SOX10.
Together, our findings delineate the importance of immune microenvironment of
melanoma tumors in determining patient survival as well as treatment response. Also,
we found epigenetic marks to be an important tool to understand the nature of
melanoma tumors.

Published papers:

Lauss, M., Donia, M., Harbst, K., Andersen, R., Mitra, S., Rosengren, F., ... &
of adoptive T cell therapy in melanoma. Nature communications, 8(1), 1738.