THE IMMUNE ENVIRONMENT OF ACUTE MYELOID LEUKEMIA
DIE IMMUNUMGEBUNG VON AKUTER MYELOIDER LEUKÄMIE

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SUMMARY

Acute myeloid leukemia (AML) is a hematopoietic stem cell neoplasm of the elderly characterized by poor outcome with only 50% of young patients and 20% of elderly patients surviving 5 years or more. In contrast to acute lymphoblastic leukemia, minimal residual disease (MRD) markers that provide therapy guidance are available only in a limited subset of AML patients. In particular, patients with presumably favorable outcome according to genetic markers often relapse or are resistant to therapy. There is therefore urgent need to identify new biomarkers in order provide therapy guidance in AML. The Becher group has initiated a comprehensive research program using single cell Cytometry by time of flight (CyTOF) to interrogate the human peripheral blood mononuclear cell compartment. Using this pipeline cellular correlates of clinical responses to T-cell immune checkpoint inhibition in the blood of melanoma patients were detected and identified a monocyte subpopulation, which strongly correlates with survival. A comprehensive analysis of AML induced changes in the surrounding immune system has not been performed so far. However, the identification of AML-specific mutations in mature T-cells and the identification of alterations in immune-related pathways by single cell gene expression analysis suggests that in AML the immune system can undergo alterations via cell intrinsic and cell extrinsic mechanisms. The impact of these alterations on AML response to therapy and outcome is unknown. Immune signatures that predict response may be integrated into the stratification of AML, particularly in the absence of predictive genetic markers. Moreover, identification of altered immune components could reveal novel actionable therapeutic targets. In this proposal we will utilize curated AML samples to 1) generate a comprehensive map of the peripheral immune compartment of a cross sectional cohort by CyTOF, to 2) study a longitudinal cohort of paired samples at baseline and after therapy, to identify stratifying biomarkers for relapses and to 3) verify the impact of stratifying signatures using a detailed functional analysis of patient mononuclear cells in vitro.