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Onco-Fetal Reprogramming in Juvenile Myelomonocytic Leukemia Upregulates Surface Markers which can be Exploited as Therapeutic Targets

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Juvenile myelomonocytic leukemia (JMML) is a myeloproliferative neoplasm of early childhood, which is driven by genetic activation of RAS signaling. JMML is characterized by a high degree of clinical heterogeneity, which can be resolved by DNA methylation patterns. However, the functional role of epigenetics in tumorigenesis remains elusive. The presence of RAS mutations at birth suggested a prenatal origin of JMML in some patients. Therefore, we hypothesized about different developmental origins of epigenetic subgroups in JMML.

In a multi-omics approach we analyzed the cellular origins of JMML subgroups and the underlying molecular programs in primary samples. Functionally, we validated our findings using genetically engineered mice and a patient-derived xenograft (PDX) model. We discovered the conservation of JMML subgroups in hematopoietic stem cells (HSCs) from JMML patients, which were associated with developmental gene regulation programs. Epigenomic dysregulation correlated with fetal-like expression signatures in HSCs from high-risk patients, whereas low-risk HSCs revealed typical postnatal marker expression.

The systematic comparison of DNA methylomes from JMML HSCs with references from fetal to adult HSCs revealed post-natal HSC states for patients of all subgroups. However, high-risk JMML HSCs exposed fetal-like methylation patterns, suggesting onco-fetal reprogramming in those patients. Therefore, we used an HSC-specific JMML mouse model to discriminate between the reactivation of fetal signatures in postnatal HSCs and the conservation of such programs due to a fetal cell-of-origin. Postnatal induction of *Ptpn11-E76K* in HSCs resulted in fetal-like expression profiles akin to those observed in high-risk JMML.

Integration of human and murine data identified several subgroup-specific HSC surface markers, which represent novel prognostic biomarkers and potential therapeutic targets for high-risk JMML. As a proof-of-principle, we functionally validated CD52-targeted therapy in a PDX mouse model. Treatment with alemtuzumab resulted in the depletion of JMML HSCs, pan-hematopoietic clearance of leukemia cells, and improved survival of 2° recipient mice.

In conclusion, onco-fetal reprogramming is a hallmark of high-risk JMML resulting in unique molecular profiles. The characterization of epitype-specific aberrations of HSCs from high-risk JMML revealed novel prognostic biomarkers and pre-clinical evidence for the efficacy of anti-CD52 immunotherapy.

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