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OC 34

ONCO-FETAL REPROGRAMMING DRIVES HIGH-RISK JUVENILE MYELOMONOCYTIC LEUKEMIA, WHICH CAN BE TARGETED BY ANTI-CD52 TREATMENT

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Background and aims: Juvenile myelomonocytic leukemia (JMML) is caused by genetic activation of RAS signaling and has a heterogeneous clinical course. JMML epitypes resolve this heterogeneity but high-risk patients lack efficient curative treatment options. To date, the mechanisms driving disease heterogeneity remain unclear. This study aimed to decipher the underlying molecular programs in order to identify disease-specific aberrations for diagnostic and therapeutic purposes.

Methods: We employed a multi-omics approach to dissect the epitype-specific molecular programs in primary JMML patient samples. Our findings were validated using an inducible *Ptpn11-E76K* knock-in mouse and a patient-derived xenotransplantation (PDX) model.

Results: Multi-modal analysis demonstrated conservation of epigenetic subgroups in hematopoietic stem cells (HSCs) of JMML patients. Epigenomic dysregulation affected binding motifs of developmental transcription factors and correlated with ectopic expression of fetal HSC signatures in high-risk patients, including *HMGA2* and fetal hemoglobin. Mapping JMML HSC methylomes onto the normaldevelopmental trajectory from fetal to adult HSCs, generally revealed a post-natal HSC state. However, high-risk JMML HSCs were epigenetically more immature and presented fetal-like methylation patterns. Employing a JMML mouse model with postnatal induction of the *Ptpn11-E76K* mutation resulted in reactivation of fetal-like expression programs in HSCs akin to those observed in high-risk JMML, suggesting that high-risk JMML HSCs hijack fetal programs. In line with this, integrative analysis identified several subgroup-specific molecular markers which might serve as prognostic biomarkers for high-risk JMML. One of those markers, CD52, was both differentially methylated and highly expressed in high-risk JMML HSCs. Targeting CD52 with alemtuzumab in a JMML PDX mouse model demonstrated reduced human engraftment in treated recipients and increased survival of 2° recipients.

Conclusions: In summary, we identified onco-fetal reprogramming as a hallmark of high-risk JMML. We determined unique molecular programs which can be used to develop new treatment strategies for high-risk JMML and provide pre-clinical evidence for anti-leukemic activity of alemtuzumab.

Keywords: JMML, Multi-OMICS, targeted treatment, biomarkers

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