Profiling the immune landscape of juvenile myelomonocytic leukaemia (JMML) reveals targets for checkpoint therapy

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Background: Juvenile myelomonocytic leukaemia (JMML) is a highly aggressive myeloid malignancy of infant and early childhood. The only curative treatment for most JMML patients is allogeneic haematopoietic cell transplantation (allo-HCT), but relapse risk remains high, especially in patients with *PTPN11* mutations. The role of immune escape in JMML remains unclear. We thus set out to understand the immune landscape and immune checkpoint expression in JMML using CyTOF profiling of JMML spleens.

Method: We performed cytometry time-of-flight (CyTOF) analysis for a comprehensive human immune profiling of adaptive and immune cell subsets using 46 markers to characterize the immune distribution and immune checkpoints of JMML spleens (n = 31) from patients with different mutation types and healthy controls (n=4).

Result: We identified several cell subtypes including T cells, B cells, NK cells, myeloid cells, stem cells and JMML cells. Analysis of immune escape molecules showed that JMML cells expressed high levels of Siglec7, Siglec9, CD47, CD39, CD33 and NXO2. Expression of checkpoint PD-1 was observed by some CD8+ T cells. We observed a skewed immune distribution among JMML subtypes. Compared with *CBL* and *KRAS* mutation, *PTPN11* mutation exhibited an increased presence of CD11b+CD11c+CD14+ myeloid cells and CD34+ stem cells. Cluster analysis revealed that PTPN11-specific myeloid immune cluster expressed several immune checkpoints including CD39, CD47, Siglec7, Siglec9 and Nox2.

Conclusion:
CyTOF analysis could identify different immune cell populations and immune signatures associated with JMML driver mutations. This information identifies potential immune targets for developing novel immunotherapeutic therapeutic approaches.