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

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Background
Juvenile myelomonocytic leukemia(JMML) is characterized by constitutive activation of the RAS signaling pathway with recurrent mutations in PTPN11, NRAS, KRAS, NF1, and CBL. Allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative treatment option. However, Patients with PTPN11 mutations always have a high relapse rate after HSCT. The mechanisms underlying the poor clinical outcomes are unknown but likely due to differential oncogenic signaling connected to immune escape.

Method
We performed cytometry time-of-flight (CyTOF) analysis for a comprehensive human immune profiling to characterize the immune distribution and immune checkpoints of paired bone marrow and peripheral blood (n=11) from patients and healthy PBMC controls(n=4).

Results
Several immune clusters were identified including NK cells, T cells, stem cells, B cells, pDC-like cells and myeloid cells in bone marrow and peripheral blood. T-SNE plots showed that JMML cells highly expressed Tim-3, CD39, Siglec7, Siglec9, CD47, CD38 and NOX2; while the expression of PD-1 and CTLA-4 was observed in some CD8+T cells. JMML$^{PTPN11\text{-}mutant}$ relapse group exhibited a notable increase in stem cells and monocytes. Furthermore, JMML $^{PTPN11\text{-}mutant}$ cells from the relapse group had a higher expression level of CD73 compared to those from the non-relapse group, but this difference was observed only in peripheral blood and not in bone marrow.

Conclusions
CyTOF analysis could identify different immune cell populations and immune signatures associated with JMML PTPN11 mutation. This information might provide potential immune targets for developing novel therapeutic approaches combining oncogenic signal inhibition and immunotherapy.