Abstract: P365

Title: TARGETING THE INTERLEUKIN-4 PATHWAY IN T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

Abstract Type: Poster Presentation

Topic: Acute lymphoblastic leukemia - Biology & translational research

Background:

Cure rates in children with T-cell acute lymphoblastic leukemia (T-ALL) approach almost 90%, due to the introduction of patient-specific intensified chemotherapy protocols in combination with stem cell transplantation. Nonetheless, this intensified therapeutic regimen coincides with severe short- and long-term side effects. Additionally, the outcome for primary therapy resistant or relapsed patients remains extremely poor. Therefore, the need for novel targeted therapies that improve the prognosis of high-risk refractory/relapsed T-ALL patients remains high.

Aims:

We identified a subset of human T-ALL patients that harbor genomic aberrations that drive abnormal interleukin-4 receptor expression that either can be activated by paracrine IL-4 present in the microenvironment or acquire the ability to produce and excrete autocrine IL-4. Therefore, we aim to study the therapeutic potential of targeting the IL-4 signaling pathway in this subset of IL-4R+ T-ALLs.

Methods:

Publicly available MicroArray and RNAseq datasets from cohorts of T-ALL patients were explored for the expression of IL-4 and IL-4Ra. These results were further validated at the protein levels on a series of Patient Derived Xenograft (PDX) T-ALL models by using ELISA, immunoblot and flow cytometric analysis. To evaluate the functionality of the IL-4R pathway, T-ALL cells were in-vitro/ex-vivo stimulated with IL-4 ligand to test the effects on downstream phospho-STAT levels via flowcytometry and target gene upregulation via RT-qPCR. Pathway stimulation was correlated with changes in ex-vivo T-ALL cell survival and proliferation using cell viability assays. Finally, therapy efficacy of IL-4 pathway blocking was evaluated either as a monotherapy or in combination with glucocorticoids on PDX models with an autocrine activated IL-4R pathway.

Results:

We identified aberrant IL-4 and IL-4Ra levels specifically in more mature molecular subgroups of T-ALL patients. Ex-vivo PDX cultures showed higher cell survival when stimulated with IL-4 ligand, which correlated with increased levels of phospho-STAT6. When administering dexamethasone in combination with an IL-4Ra blocking antibody or phospho-STAT6 inhibition, a synergistic effect was found in ex-vivo culture in the presence of IL-4 stimulus. Monotherapy with IL-4Ra blockage in-vivo, showed a significant effect on the progression of an IL-4+ T-ALL PDX model, as demonstrated by reduction of circulating blasts in the peripheral blood (Figure).

Summary/Conclusion:

Interleukin-4 in the microenvironment provides IL-4R+ T-ALL cells with a survival and proliferative advantage, which could ultimately drive prolonged survival of cancer cells and reduced sensitivity towards glucocorticoids. Blocking this pathway with an antibody against IL-4Ra reverts this effect, and sensitizes the cells to dexamethasone treatment.

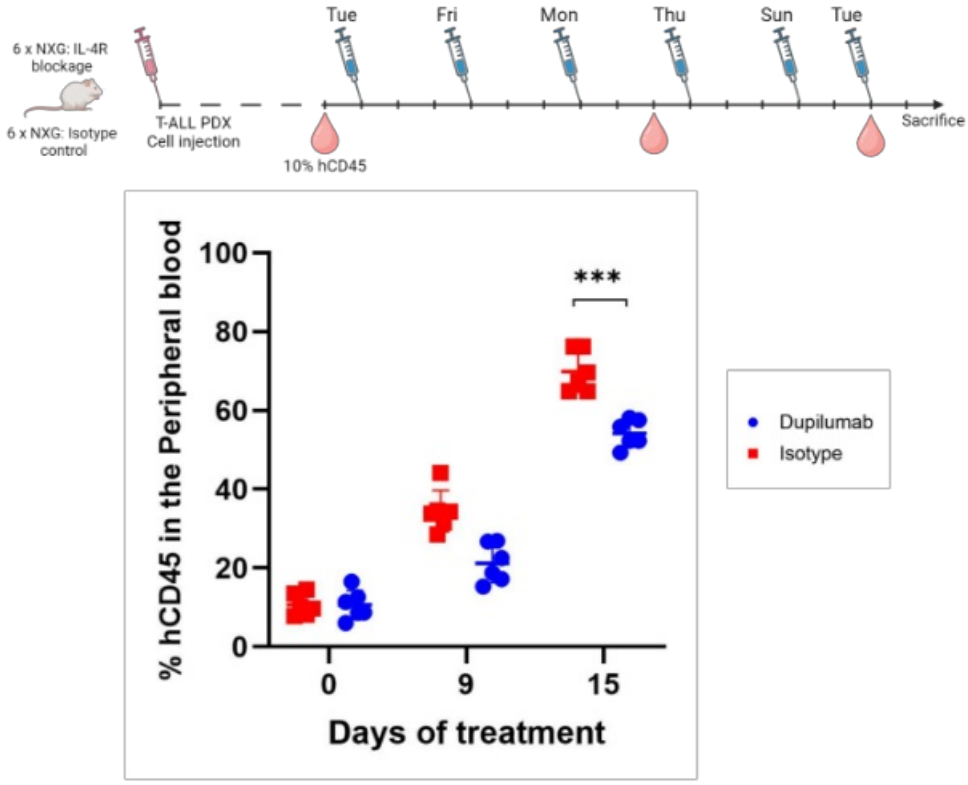

Figure: Treatment of T-ALL PDX model in-vivo with 25mg/kg IL-4R blocking antibody or Isotype control every other two days, for two weeks – 6 mice per group. The percentages of hCD45+ cells was detected by flowcytometry in the peripheral blood of each mice at 3 time points.

Keywords: Microenvironment, T-ALL