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POSTER ABSTRACTS

603.LYMPHOID ONCOGENESIS: BASIC

A Dual Role of SOX11 Expression in the Formation of T-Cell Acute Lymphoblastic Leukemia in Mouse Models

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Introduction: T-cell acute lymphoblastic leukemia (T-ALL) is an aggressive hematological malignancy that accounts for 10%-15% of pediatric and 25% of adult ALL cases. Intensified chemotherapy and bone marrow transplants have improved the survival of T-ALL patients. However, around 20% of patients still suffer from primary resistant or relapsed T-ALL. Therefore, improving our knowledge of T-ALL biology and developing precision oncology therapeutics is essential for further progress in T-ALL treatment.

SRY-related HMG-box 11 (SOX11) is a transcription factor that regulates the development and survival of multiple embryonic tissues and is crucial for the nervous system. SOX11 is expressed in a multitude of tumor types, where it has been associated with either increased or decreased cell proliferation, metastatic potential, and with either good or bad prognosis, depending on cancer type. Despite being absent in the T-cell lineage, SOX11 is expressed in a subset of T-ALLs, where it plays an unknown role. Based on having a malignantly restricted expression, we hypothesize that SOX11 might be oncogenic in T-ALL.

Aim: Identify the role of aberrant SOX11 expression in (pre)leukemic T-cells.

Methods: Using a conditional *Rosa26-SOX11* overexpression mouse model, we generated mice with T-cell specific (using *Lck-cre*) SOX11 expression (SOX11 ^{Lck}). To assess the self-renewal potential of SOX11 ^{Lck} thymocytes, we performed thymic transplantations on sublethally irradiated mice expressing a different allele of CD45. To study SOX11 in a leukemic context, we crossed the SOX11 ^{Lck} mice with two established T-ALL mouse models that are either driven by the overexpression of Lmo2 (SOX11 ^{Lck}-Lmo2 ^{CD2}) or by the loss of the tumor suppressor Pten (SOX11/Pten ^{Lck}). An aging cohort of these T-ALL models was followed, and tumor samples were collected. Thymi of 8-weeks old mice were used to study the impact of SOX11 in a pre-leukemic context, and T-cell tumors arising in these models were also used for RNA-sequencing. Using a retroviral strategy, we overexpressed SOX11 in human cord blood stem cells, which we differentiated towards the T-cell lineage ex vivo by co-culturing them on OP9 stromal cells expressing Delta-like Notch ligand 4. Furthermore, we transduced Jurkat cells with a SOX11 expression vector, or with an empty vector, and injected the cells into immunocompromised mice to assess the effect of SOX11 on tumor growth in vivo.

Results: In SOX11 ^{Lck} mice, we found a significant increase in the immature double-negative 3 (DN3) thymic fraction, with a concomitant decrease in the amount of more mature double-positive CD4 $^{+}$CD8 $^{+}$ (DP) thymocytes (Fig. A). A possible explanation for this phenotype would be the establishment of a stem-like self-renewal program similar to the one driven by Lmo2. However, by performing thymic transplantations into sublethally irradiated mice, we concluded that SOX11 does not confer self-renewal properties to thymocytes. Additionally, we aged a cohort of SOX11 ^{Lck} mice and did not observe formation of T-cell malignancies up to 500 days of age. Given that the expression of SOX11 does not suffice to produce T-cell tumors, we generated the SOX11 ^{Lck}-Lmo2 ^{CD2} and SOX11/Pten ^{Lck} T-ALL mouse models. In SOX11 ^{Lck}-Lmo2 ^{CD2} mice, we found a synergistic effect of the co-expression of both genes on the expansion of DN3 thymocytes (Fig. A), which led to accelerated leukemia formation (Fig. B). By sequencing the RNA of pre-leukemic and leukemic DN3 cells, we observed that SOX11 is mostly regulating cell adhesion, morphology, and cell-cell interactions to promote this oncogenic phenotype in Lmo2-driven T-ALL. On the other hand, SOX11/Pten ^{Lck} mice suffered from delayed leukemogenesis (Fig. B), and this tumor suppressor role might be associated with the decrease in DP cells observed in the pre-leukemic stage. Lastly, we set out to validate these findings in a human context. The ex vivo differentiation of human hematopoietic stem cells toward the T-cell lineage showed that SOX11 strongly accelerates early commitment to double-negative T-cell precursors. Also, we observed that Jurkat T-ALL cells engraft faster in immunocompromised mice when expressing SOX11.

Conclusions: By generating multiple models of SOX11 expression in the T-cell lineage, we showed that SOX11 impacts T-cell differentiation, both in mice and humans, and that it can promote or hinder T-ALL formation depending on the oncogenic driver.

Disclosures No relevant conflicts of interest to declare.

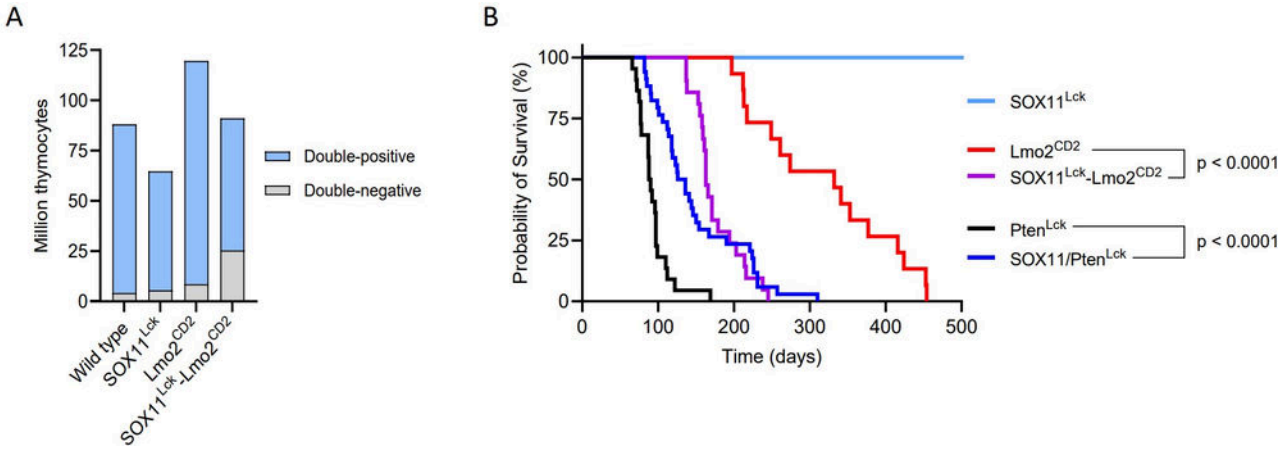

Figure 1

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