The TLX1 oncogene modulates the enhancer RNA landscape in T-ALL

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T-cell acute lymphoblastic leukemia (T-ALL) is an aggressive type of blood cancer resulting from malignant transformation of T-cell precursors. Several driver oncogenes, including the TLX1 transcription factor, have been identified as early events that cooperate with other genetic aberrations in the leukemic transformation of progenitor T-cells. Previously, we established the TLX1 regulome and enhancer landscape revealing a crucial role in regulation of superenhancer sites integrating polyA and total RNA-sequencing data of ALL-SIL lymphoblasts upon TLX1 knockdown with TLX1 and H3K27ac ChIP-sequencing. In addition, our study provided the first insights to an unanticipated transcriptional antagonism between TLX1 and another key T-ALL oncogene NOTCH1, providing a working model for the previously described delay in leukemia onset in a TLX1 transgenic mouse model. We are currently expanding the dissection of the TLX1 regulome towards long non-coding RNAs (lncRNAs). We observed a strong association of TLX1 to enhancer lncRNAs (eRNAs) sites and we are further refining this enhancer landscape through open chromatin mapping (ATACseq), H3K4me1 and H3K4me3 ChIP-sequencing as well as mapping of MED1 and RNAPII binding to these enhancers. This approach is supporting our identification of TLX1 controlled enhancer transcripts implicated in suppression of several key tumor suppressors, currently under further investigation using 4C-sequencing and LNA-mediated transcriptional modulation. This works offers perspectives for developing novel therapies aimed at transcriptional reactivation of these suppressor genes.