The T-ALL oncogene TLX1 controls enhancer lncRNA expression

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Introduction: T-cell acute lymphoblastic leukemia (T-ALL) is a genetically heterogeneous cancer. Several driver oncogenes, including the TLX1 transcription factor, have been identified as early events that cooperate with other genetic aberrations towards full leukemogenesis. Recently, we established the TLX1 regulome and enhancer landscape for protein coding genes. An unanticipated downregulation of NOTCH1 and its target genes was observed explaining delayed leukemia formation in a TLX1 transgenic mouse model (Durinck et al., Leukemia, 2015). In this study, we expanded the dissection of the TLX1 regulome towards long non-coding RNAs (lncRNAs).
Experimental procedures: We performed polyA and total RNA-sequencing following TLX1 knockdown in the ALL-SIL cell line and for a primary cohort of 64 T-ALLs, including 5 TLX1+ and 12 TLX3+ cases and also made use of our previously established TLX1 and H3K27ac ChIPseq data for further data mining.
Results: We observed a strong association of TLX1 bound enhancers and expression of lncRNAs from these enhancer sites. We observed an unanticipated down regulation of the majority of TLX1 controlled lncRNAs while TLX1 mainly acts as a repressor of protein coding genes. To further investigate this unexplained relationship for TLX1 controlled lncRNA and protein coding gene expression, we are performing LNA-mediated lncRNA knockdown in combination with 4C-sequencing in order to explore the topological regulatory interactions between TLX1 regulated lncRNAs and their presumed cis-regulatory target genes.
Conclusion: In conclusion, we established a comprehensive delineation of the TLX1 controlled regulome and provide the first evidence for a previously unestablished role of (enhancer) lncRNAs in the TLX1 epigenetic regulatory network.