TARGETING THE TRANSCRIPTIONAL NETWORK ARCHITECTURE DRIVEN BY THE ONCOGENIC TCF3-HLF FUSION

TRANSKRIPTIONELLE NETZWERK-ARCHITEKTUR ALS THERAPIEZIEL BEI TCF3-HLF–POSITIVER AKUTER LYMPHOBLASTISCHER LEUKÄMIE (ALL)

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SCHLAGWÖRTER – CHROMATINARCHITEKTUR, TRANSKRIPTIONELLE NETZWERKE, TRANSKRIPTIONELLE ABHÄNGIGKEITEN, ONKOGENE, CHROMOSOMALE TRANSLOKATIONEN, TRANSKRIPTIONSFAKTOREN, KREBSGENOMIK, LEUKÄMIE, PRÄZISIONSMEDIZIN

SUMMARY

Cancer initiating events often target fundamental mechanisms of transcriptional regulation. Chromosomal translocations resulting in oncogenic fusion transcription factors (TFs) involving hematopoietic master regulators are frequent in acute leukemias. Here we propose to map the enhancer-promoter loop architecture that is underlying the oncogenic activity of the TCF3-HLF fusion in t(17;19) positive acute lymphoblastic leukemia, a paradigm of resistant disease. After epitope tagging the endogenous TCF3-HLF by CRISPR engineering of leukemia cells, we mapped the sites of the HLF DNA binding domain portion of TCF3-HLF to less than 500 enhancer regulatory regions in the genome by ChIP-Seq, deciphered a recurrent TF binding site motif grammar and gathered information about the TCF3-HLF complex composition by immunoprecipitation followed by Mass- Spectrometry. Integration of this information with gene expression data from TCF3-HLF knockdown experiments yielded a list of candidate TCF3-HLF target genes, including MYC, which we have shown to be crucial for leukemia maintenance and propagation depending on one single HLF binding site in a MYC super-enhancer. Based on the premise that TCF3-HLF hijacks parts of a program normally driven by HLF in stem and immature progenitor cells, we aim to identify the relevant direct transcriptional targets that besides MYC drive this very aggressive leukemia. Joining the expertise of the Santoro lab and the patient-derived models of the Bourquin lab, we propose to use ChIA-PET, a technique that combines chromatin immunoprecipitation and chromosomal conformation capture, to understand the Enhancer-Promoter(s) network configuration of this leukemia. We will then subject the candidate targets to functional genetic evaluation using a platform that is established in the Bourquin lab. Having then the knowledge of the key transcriptional signature, we will screen for bioactive and therapeutic agents that can directly interfere with the oncogenic program of TCF3-HLF and validate new concepts using our in vivo leukemia xenograft model. This knowledge can then be related to normal hematopoiesis and leukemia more in general.