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Chronic myeloid leukemia

SETD2 LOSS IN CHRONIC MYELOID LEUKEMIA PROMOTES METABOLIC REPROGRAMMING AND GENOMIC INSTABILITY LEADING TO THERAPEUTIC RESISTANCE AND DISEASE PROGRESSION

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Chronic myeloid leukemia (CML) is driven by the Ph chromosome, but additional genetic abnormalities (AGAs) such as ASXL1 mutations and other cytogenetic alterations contribute to poor prognosis and reduced treatment response. SETD2 plays a critical role in DNA repair and chromatin integrity and its non genomic loss-of-function (LOF) has been linked to disease progression in CML. This study examines how SETD2 LOF impacts on CML pathogenesis and its potential as a biomarker for high-risk disease.

To investigate the role of SETD2 LOF in CML, cellular models with SETD2 silencing or overexpression were compared using liquid chromatography-tandem mass spectrometry (LC-MS/MS), RNA sequencing (RNA-seq), and chromatin immunoprecipitation sequencing (ChIP-seq). Validation was performed by Western blotting (WB), immunofluorescence (IF), and co-immunoprecipitation (co-IP) in proper cell fractions. Additionally, SNP-array analysis provided genomic insights.

Differential transcriptomic profiling revealed SETD2-dependent transcriptional regulation of genes involved in DNA repair (MSH2, MSH6) and metabolic homeostasis (PFKP, LDHA, PDK1) (FIGURE 1A). Differential interactome profiling by LC-MS/MS identified SETD2 interactions with proteins critically involved in mismatch repair (MSH2, MSH6), cell division (α-/β-tubulin), and glycolysis (PFKP, PFKFB3, PD, and LDHA). Notably, SETD2 was also found to interact with key kinases regulating proliferation and stress response, including ERK1/2 and p38 MAPK. Integration of SNP-array analysis after chronic cell exposure to DNA damaging agents with ChIP-seq of SETD2-dependent H3K36me3 deposition sites confirmed that SETD2 plays a direct role in promoting faithful DNA damage response, since breakpoints were enriched at sites where H3K36me3 was disrupted by SETD2 LOF.

Notably, we uncovered a novel role for SETD2 LOF in rewiring cellular metabolism: SETD2 re-expression attenuated the glycolytic shift observed in SETD2-deficient cells, as evidenced by downregulation of glycolytic enzymes (FIGURE 1 B, C, D), mitochondrial oxidative phosphorylation and overexpression of IDH1 enzyme which regulates a key step in the TCA, produces NADPH and protects cells from reactive oxygen species, acting as an antioxidant.

Finally, SETD2/H3K36me3 deficiency as assessed by WB in total leukocytes could be detected in pts with AGAs at diagnosis and could discriminate pts who subsequently achieved non-optimal vs optimal responses to IM.

Our findings point to SETD2 LOF as a key cooperating event in CML, that may act since diagnosis to set the stage for TKI resistance and disease acceleration by:

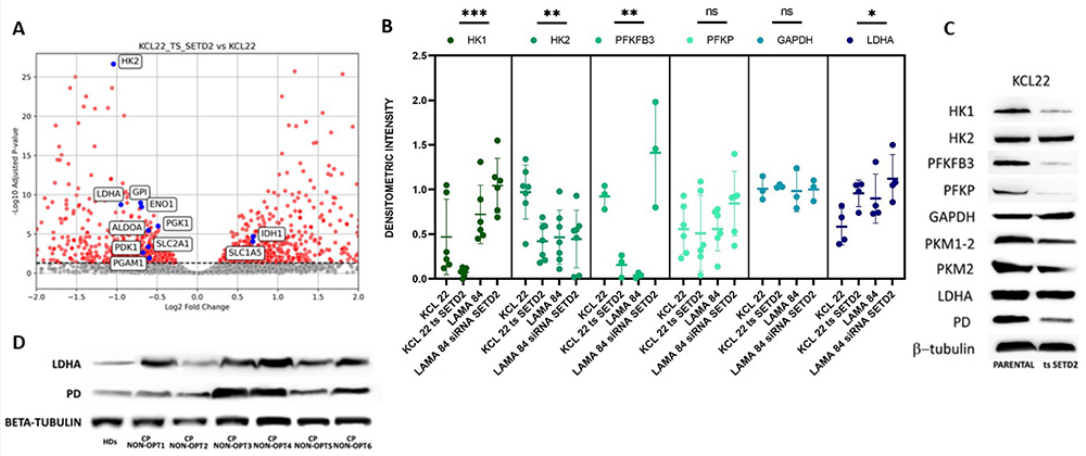
• sustaining BCR::ABL1-independent genomic instability that fuels the acquisition of AGAs

• metabolic reprogramming towards glycolysis

Whether SETD2 LOF may serve as a biomarker of high-risk disease at diagnosis is an intriguing hypothesis that we are currently exploring in a larger cohort of uniformly treated pts.

CHRONIC MYELOID LEUKEMIA

FIGURE 1



RNA-seq of SETD2-deficient (KCL22) and -proficient (KCL22 tsSETD2) cells and WB validation of expression data.
A: Volcano plot: the log2 fold change (FC) represents the change in expression between the two conditions for each gene. Each dot corresponds to a single gene, with red dots indicating genes that are significantly differentially expressed, and blue dots highlighting genes of interest. **B**: Scatter plot representing select glycolytic enzyme levels, estimated by densitometric analysis of WB using ImageJ software. Protein signal intensities from individual blots were normalized to β-tubulin levels and averaged. The means of six experiments and p-values were calculated using GraphPad software. A nested t-test was used to compare paired data (KCL22 parental vs. KCL22 ts SETD2)(***: p-value <0.001; **: p-value <0.01; *: p-value<0.05; ns: not significant). **C**: Representative WB results showing protein levels of the same glycolytic enzymes in KCL22 parental and SETD2-transfected cell lines. A representative blot from one of six independent experiments is shown. **D**: WB and densitometric analysis performed using total lysates from samples collected at diagnosis from 6 non-optimal responders to imatinib, showing SETD2 deficiency, revealed PD and LDHA levels from 3 to 33-fold higher as compared to healthy donors.