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Project Title	Molecular signature of hematopoietic aging
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Report

Resistance to treatment is due to the heterogeneity of the tumor which contains a subset of cancer cells that escape treatment and are responsible for the relapse. We took advantage of the PLZF/RARA retinoic acid (RA) resistant acute promyelocytic leukemia (APL) model to catch relapse-initiating cell features and their vulnerabilities. By developing an integrative single-cell multi-omics analysis (scRNA-seq and scATAC-seq), we uncovered transcriptional and chromatin heterogeneity of the PLZF/RARA APL blasts. We highlighted a subset of cells insensitive to RA-induced differentiation with a strong DNA repair signature ("Rep" cluster) and exhibiting a fine-tuned transcriptional network targeting the histone methyltransferase Ezh2. Combining epigenomic profiling with mouse-derived models for Ezh2 catalytic inhibition or total KO, we revealed an independent methyltransferase Ezh2 activity linked to RA resistance. These findings demonstrate the power of single-cell multi-omics integration to highlight paths to sensitize therapy-resistant leukemia cells.