The H3K27ac enhancer landscape is associated with the baseline differentiation state of the oncogenic RARα known factors important for maintaining an immature/proliferative state were found associated with enhancers most deactivated by SY-1425 (as upregulation α mediated differentiation block of RARA-high AML).

Consistent with the observed epigenomic alterations. Comparable changes were not found in RARA-low AML cell lines. This effect supports the differentiation of THP-1 as dendritic cells, granulocytic cells, and macrophages. This was in contrast to the well-treated. We find that the enhancer landscape of RARA-high AML cell lines was changed by SY-1425 toward one resembling more fully healthy human immune cells comprising hematopoietic stem and progenitor cells (HSPCs) as well as multiple myeloid lineages.

Here, we profile the non-coding genome and transcriptional landscape in AML cells to define the circuitry of RARA-high AML characterized by currently being evaluated in a biomarker directed Ph2 clinical study in AML and MDS. A subset of AML and MDS patients, referred to as RARA-1a, are sensitive to SY-1425 (THP-1, OCI-AML3, MV4-11, and EOL-1) tend to be most similar to monocytes, while RARA-low cell lines those without (RARA-low) are insensitive.

The percent of H3K27ac enhancers induced upon SY-1425 treatment by whether they are bound by RARα.

Conclusions

- SY-1425 drives RARA-high AML cell lines towards more differentiated cell types.
- RARα has a significant role in the gene regulatory circuit of SY-1425 response.
- Other TFs, such as IRF8, are part of the circuitry of response to SY-1425.
- A biomarker-directed phase 2 trial (NCT02807558) of SY-1425 is currently ongoing in genomically defines subsets of AML and MDS patients.