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POSTER ABSTRACTS

621.LYMPHOMAS: TRANSLATIONAL-MOLECULAR AND GENETIC

GATA-3 Dependent Gene Transcription Is Impaired upon HDAC Inhibition

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Background: GATA-3 is a lymphoid-lineage specific zinc-finger transcription factor that plays a pivotal role in the development and homeostatic survival of thymic T-cell progenitors and subsets of their mature progeny. Diverse T-cell lymphomas (TCL), derived from conventional (non-malignant) T cells expressing GATA-3, highly express GATA-3 and a GATA-3 dependent transcriptional program, and are generally associated with poor outcomes. Upon binding gene enhancers and promoters, GATA-3 regulates gene transcription, including those with cell-autonomous (e.g. oncogenes, including c-Myc) and non-cell-autonomous (e.g. type 2 cytokines) functions in TCL. Therefore, GATA-3, and the transcriptional program it instigates, is a bona-fide proto-oncogene in these lymphomas. GATA-3 acetylation is dynamically regulated, and its acetylation controls its DNA binding affinity and target gene expression. Therefore, we sought to examine the extent to which HDAC inhibition may alter GATA-3 acetylation and functionally regulate its DNA binding capacity and target gene expression in CTCL.
Methods: Integrated GATA-3 ChIP-seq and RNA-seq was performed in CTCL cell lines and primary specimens treated with clinically available HDACi. Complementary strategies were utilized to examine GATA-3/HDAC binding and GATA-3 acetylation in these cells.
Results: In order to investigate early transcriptional changes upon HDACi treatment, a well characterized CTCL cell line (H9) and primary Sezary Syndrome (SS) specimens (n=3) were transcriptionally profiled. Gene set enrichment analysis (GSEA) was performed using the differentially expressed genes we identified, and a convergence on relevant T-cell growth and survival pathways was observed. GATA-3 target genes were differentially expressed upon HDACi treatment, and binding sites for GATA-3, and transcription factors (TF) it transcriptionally regulates, were enriched among HDACi responsive genes. Among the 5,510-6,811 transcripts that were differentially expressed upon either belinostat or romidepsin treatment, respectively, ≈6-7% of transcripts were GATA-3 targets. GATA-3 dependent transcripts were significantly altered upon treatment with belinostat or romidepsin in primary SS specimens.
We next examined the association between GATA-3 and class I HDACs in CTCL cell lines. HDAC1/HDAC2 and GATA-3 binding was observed, suggesting that HDAC inhibition may lead to GATA-3 hyperacetylation. Treatment with the three clinically available HDACi led to a significant increase in GATA-3 acetylation. As GATA-3 acetylation regulates its ability to bind DNA and regulate transcription, we examined GATA-3 DNA binding using orthogonal approaches, including GATA-3 ChIP-seq, and a significant reduction in GATA-3 binding peaks was observed, culminating in significant changes in the GATA-3 dependent transcriptome.
Conclusions: Collectively, these findings demonstrate that GATA-3 hyperacetylation upon HDAC inhibition significantly impairs GATA-3 DNA binding and GATA-3 dependent gene transcription.
Impact: GATA-3 and its target genes identify clinically and transcriptionally distinct T-cell lymphomas, including CTCL, that are resistant to conventional chemotherapeutic agents and generally associated with dismal outcomes. Therefore, GATA-3 is a rational, albeit challenging, therapeutic target in these T-cell lymphomas. We have previously explored "upstream" strategies to target GATA-3 by exploiting transcription factors that regulate its expression, and have more recently explored "downstream" strategies by targeting its target genes, including ITK. To the best of our knowledge, the work described here is the first - and a clinically approved - strategy to therapeutically target GATA-3 directly, as HDACi significantly increase GATA-3 acetylation, and by doing so, impair its ability to bind DNA and regulate transcription of its gene targets. Consequently, these findings have significant implications for the interpretation of existing clinical trial datasets and for the development of future combinatorial strategies utilizing an HDACi-containing backbone in GATA-3 driven T-cell lymphomas.

Disclosures No relevant conflicts of interest to declare.

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