2026 EHA Abstract

Title:
Exploring the epigenetic role of PRDM1: a target for IMiD-resistant Multiple Myeloma?

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Background:
Multiple myeloma (MM) is an incurable plasma cell malignancy that accounts for 15% of all blood cancers. Immunomodulatory drugs (IMiDs) are a first-line treatment for MM and patients have often developed resistance to them at relapse. IMiDs operate by degrading the key transcription factors (TFs) IKZF1/Ikaros and IKZF3/Aiolos, which play a pivotal role in transforming terminally differentiated plasma cells into actively dividing myeloma cells. The degradation of these TFs is commonly blocked in IMiD-resistant patients, meaning relapse myeloma cells remain dependent on their IKZF1/3. PRDM1 is another key TF, which is known to heterodimerise with IKZF1/3, suggesting that it may provide an alternative therapeutic target to disrupt their activity in IMiD-resistant patients. PRDM1 has counterintuitive roles in both plasma cell differentiation and MM proliferation, and it is unclear how its behaviour is altered in MM to promote myelomagenesis.

Aims:
To investigate the role of PRDM1 alongside IKZF1/3 in MM to assess its potential as a novel therapeutic target in IMiD-resistant patients.

Methods:
We used ChIP-seq to map PRDM1 and IKZF1/3 binding in MM cell lines. ChIP-seq for histone H3K27 acetylation (H3K27ac) was used to identify active enhancers and promoters. We introduced an FKBP12^{F36V} degron tag to the endogenous PRDM1 in MM1S cells, allowing rapid, inducible degradation, followed by transient transcriptome sequencing (TT-seq) to look at immediate effects on transcription, and ChIP-seq for TFs and histone acetylation (H3K27ac). This was compared to the effects of IKZF1/3 degradation with the IMiD pomalidomide.

Results:
PRDM1 displayed widespread enhancer and promoter binding, including at key oncogenes, and degradation of PRDM1 resulted in both up- and downregulated transcription. Upregulated genes, especially those bound by IKZF1/3, were strongly enriched for PRDM1 binding, supporting a direct repressive role at these targets. In support of this, H3K27ac, a mark of activation, increased dramatically at both enhancers and promoters of the upregulated genes, following PRDM1 degradation. Downregulated genes were also bound by PRDM1, although with bias towards enhancer binding, arguing for a parallel role in gene activation. ChIP-seq showed co-occupancy with IKZF1/3 at many loci, including differentially expressed genes. Overlap of differential genes following PRDM1 or IKZF1/3 degradation identified genes that were

dependent on the continued presence of both factors. Interestingly, IKZF3 binding was seen to decrease following PRDM1 degradation, arguing that IKZF3 may be dependent on PRDM1 for continued chromatin binding. Notably, combined treatment with dTAG to induce PRDM1 degradation and the IMiD pomalidomide resulted in a greater reduction in cell growth compared to either treatment alone.

Conclusion:
This work suggests a MM gene regulatory network coordinated by PRDM1 and IKZF1/3, with the activity of PRDM1 influenced by binding to IKZF1/3 and vice versa. This argues that targeting PRDM1 in IMiD-resistant patients could disrupt the same transcriptional networks that IMiDs successfully block, providing alternative treatment options for relapse patients.