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RBM15 and ZMYND8 shape acute myeloid leukemia response to BCL2 inhibitors

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The introduction of the BCL2 inhibitor venetoclax has significantly improved frontline treatment options for acute myeloid leukemia (AML), particularly in older patients and those unfit for intensive chemotherapy. However, clinical resistance, both primary and acquired, remains a persistent challenge, often driven by transcriptional rewiring that shifts dependency away from BCL2 toward other anti-apoptotic proteins such as MCL1 or BCL2L1 (BCL-XL)[1,2]. In this issue of Haematologica, Brim-Edwards et al. address this clinical and biological problem by identifying novel shared mediators of resistance to both venetoclax and the dual BCL2/BCL2L1 inhibitor AZD4320, thereby extending our understanding of apoptotic plasticity and its regulation in AML[3].

Using genome-wide CRISPR screens and integration with primary patient data, the authors systematically explored both shared and distinct genetic dependencies governing response to BCL2-targeting agents. Their analysis of 232 primary AML samples confirmed that ex vivo responses to venetoclax and AZD4320 are highly correlated at the gene expression level, suggesting that overlapping biological pathways mediate response to both agents.

To functionally define these mechanisms, the authors performed genome-wide CRISPR knockout screens in OCI-AML2 cells treated with AZD4320. While known apoptotic regulators such as PMAIP1, BAX, TP53, and BCL2L1 emerged as expected hits, the screen identified RBM15 and ZMYND8 as previously undescribed, tier 1 regulators of resistance to both venetoclax and AZD4320. Loss of either gene conferred specific resistance to BCL2 inhibitors, without affecting response to unrelated drugs such as trametinib or midostaurin, highlighting their unique roles in modulating apoptotic sensitivity.

RBM15, an RNA-binding protein involved in N6-methyladenosine (m^6A) RNA methylation[4], and ZMYND8, a reader protein associated with the NuRD chromatin remodeling complex[5], emerged as gatekeepers of drug sensitivity through their regulation of AML differentiation and apoptotic balance. RBM15 knockout did not alter levels of classic pro-survival proteins (e.g., MCL1 or BCL2A1), but instead shifted apoptotic priming through downregulation of BIM (BCL2L11), a key pro-apoptotic initiator. Conversely, ZMYND8 knockout reduced BCL2 expression relative to MCL1 and BCL2A1, suggesting a reprogramming of anti-apoptotic dependencies.

These functional changes were accompanied by transcriptional profiles indicative of monocytic differentiation, a state previously associated with innate resistance to venetoclax. Indeed, both RBM15- and ZMYND8-deficient cells showed gene expression signatures enriched for macrophage-like, monocytic-like, and dendritic-like states. In parallel, analysis of patient samples demonstrated that lower expression of RBM15 and ZMYND8 correlates with higher peripheral blood monocyte counts, reinforcing the link between differentiation and resistance.

To understand these effects at a systems level, the authors moved beyond single-gene metrics to assess m^6A and NuRD complex activity as integrated pathways. Using principal component analysis (PCA) of RNA-seq and proteomic data, they developed eigengene-like activity scores (PC1s) for each complex. Reduced pathway activity associated with increased differentiation (higher monocytes, fewer blasts) and decreased ex vivo sensitivity to both venetoclax and AZD4320. These composite signatures not only reinforce the biological role of these pathways but may also serve as biomarkers of drug response.

This study offers several key insights: 1) Identification of shared resistance mechanisms: RBM15 and ZMYND8 act as shared dependencies for response to venetoclax and AZD4320, linking RNA methylation and chromatin remodeling to therapeutic efficacy. 2) Divergent mechanisms of resistance: Despite converging on drug resistance, RBM15 and ZMYND8 act via distinct apoptotic rewiring strategies, either by altering pro-apoptotic signaling (BIM) or shifting anti-apoptotic dependencies. 3) Cell state-dependent resistance: Differentiation toward monocytic phenotypes, driven by reduced m^6A or NuRD activity, emerges as a unifying feature of resistance. 4) Translational relevance: these findings could inform predictive biomarkers and highlight potential targets for combination therapy aimed at re-establishing apoptotic sensitivity.

Despite these important advances, several questions remain. First, the mechanistic studies rely largely on a single AML cell line, and it will be important to determine whether RBM15- and ZMYND8-dependent resistance mechanisms are conserved across genetically diverse AML contexts. Second, while analyses of primary patient samples support the association between reduced m^6A and NuRD pathway activity, monocytic differentiation, and drug resistance, direct functional validation in primary AML cells would strengthen the causal link between these processes. In addition, the downstream molecular circuits by which RBM15 and ZMYND8 regulate apoptotic priming remain incompletely defined, particularly in the case of RBM15, where resistance appears to be mediated through reduced BIM expression rather than classical shifts in anti-apoptotic dependencies. Finally, an important unresolved question is whether diminished m^6A and NuRD activity actively drives differentiation and resistance, or instead reflects pre-existing cell states that are intrinsically less sensitive to BCL2 inhibition. Addressing these questions will be critical for translating these insights into improved treatment strategies.

By focusing on shared and unique regulators of resistance across BCL2-targeted agents, Brim-Edwards et al. provide a novel framework for understanding how AML cells adapt to evade apoptosis. Their integration of CRISPR screening, patient-derived transcriptomes, and pathway-level analysis represents a powerful paradigm for uncovering the epigenetic and transcriptional basis of therapy response.

As venetoclax-based therapies expand in AML and beyond, the ability to anticipate, detect, and overcome resistance will become increasingly important. This work not only deepens our understanding of AML biology but also charts a path toward more durable and personalized therapeutic strategies.

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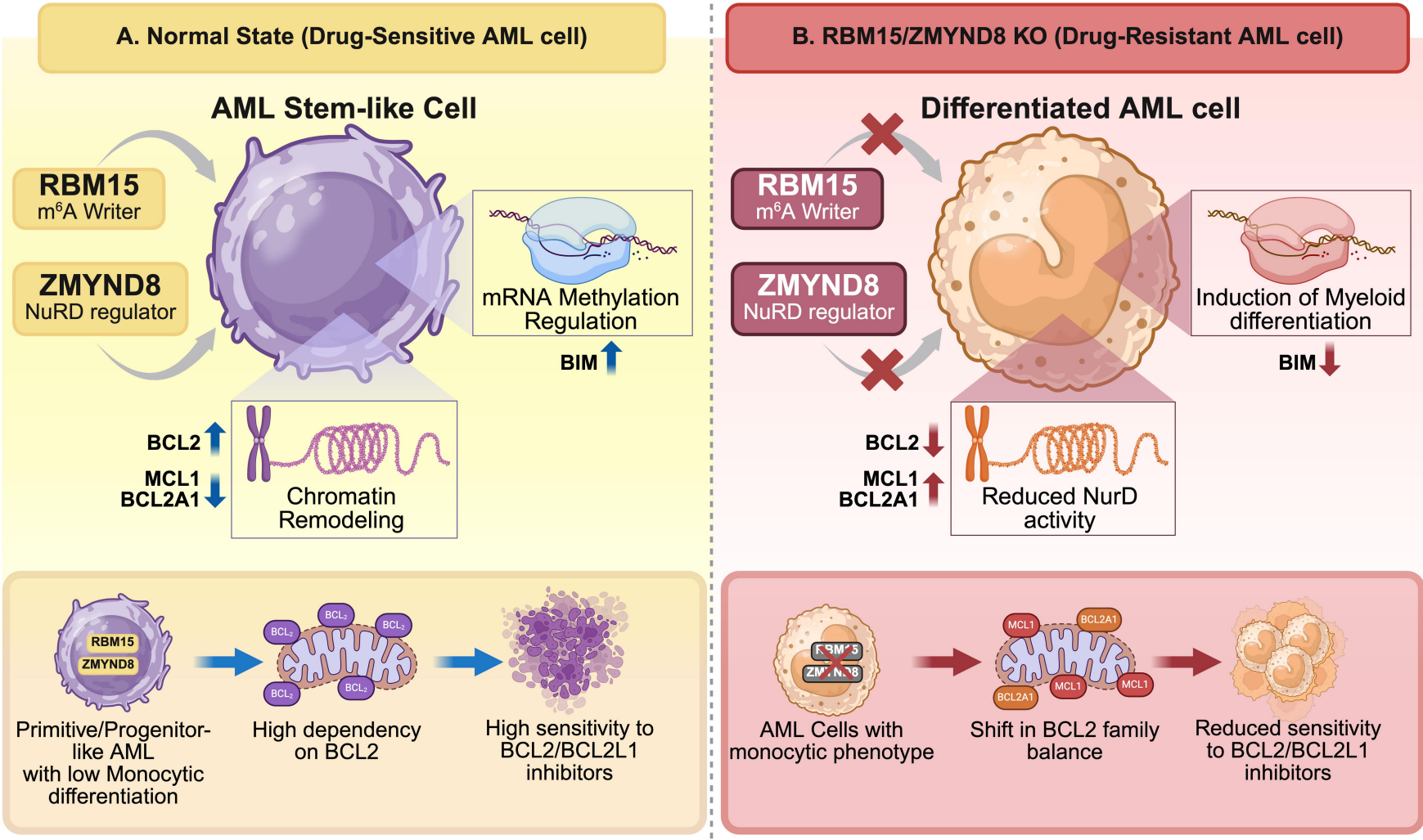
FIGURE LEGENDS

Figure 1. Epigenetic and post-transcriptional regulation of BCL2 inhibitor sensitivity in AML.

This schematic illustrates the proposed model by which RBM15 and ZMYND8 regulate sensitivity to BCL2 family inhibitors in acute myeloid leukemia (AML). In the drug-sensitive state (left), RBM15 and ZMYND8 maintain high activity of the m^6A RNA methylation machinery and the NuRD chromatin remodeling complex, respectively. These pathways help preserve a primitive, progenitor-like AML cell state with high BCL2 expression and pro-apoptotic BIM activity, resulting in apoptotic priming and responsiveness to BCL2 inhibitors such as venetoclax and AZD4320.

In contrast, loss of RBM15 or ZMYND8 (right) reduces m^6A and NuRD pathway activity, promoting transcriptional programs associated with monocytic differentiation. ZMYND8-deficient cells downregulate BCL2 relative to MCL1 and BCL2A1, while RBM15-deficient cells exhibit reduced BIM expression, shifting the apoptotic balance toward survival. These changes confer resistance to BCL2-targeted therapies, in part by altering dependency on anti-apoptotic BCL2 family members and reducing apoptotic priming.

Together, these findings highlight RBM15 and ZMYND8 as critical regulators of AML cell state and therapeutic response, linking epigenetic and post-transcriptional mechanisms to drug sensitivity.


A. Normal State (Drug-Sensitive AML cell)
AML Stem-like Cell
RBM15
m6A Writer
ZMYND8
NuRD regulator
mRNA Methylation Regulation
BIM
BCL2
MCL1
BCL2A1
Chromatin Remodeling
RBM15
ZMYND8
Primitive/Progenitor-like AML with low Monocytic differentiation
BCL2
High dependency on BCL2
High sensitivity to BCL2/BCL2L1 inhibitors
B. RBM15/ZMYND8 KO (Drug-Resistant AML cell)
Differentiated AML cell
RBM15
m6A Writer
ZMYND8
NuRD regulator
Induction of Myeloid differentiation
BIM
BCL2
MCL1
BCL2A1
Reduced NurD activity
AML Cells with monocytic phenotype
MCL1
BCL2A1
Shift in BCL2 family balance
Reduced sensitivity to BCL2/BCL2L1 inhibitors