

PRKCE maintains BCR signaling dependency and cell-cycle adaptation to drive BTK inhibitor resistance in Waldenström Macroglobulinemia

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Background:

Waldenström macroglobulinemia (WM) is an indolent B-cell malignancy characterized by bone marrow infiltration of lymphoplasmacytic cells and monoclonal IgM secretion. Bruton tyrosine kinase inhibitors (BTKi) have significantly improved outcomes for patients with WM; however, heterogeneous response, residual disease, and acquired resistance remain clinical challenges. Therapeutic options after BTKi failure are limited, highlighting the need to identify molecular dependences that sustain WM survival during BTK inhibition and develop rational treatment strategies.

Methods and Results:

To identify molecular drivers associated with BTKi tolerance, we integrated paired pre- and post-BTKi single-cell RNA sequencing profiles from WM patient samples with published transcriptional signatures from ibrutinib non-responders. This integrated analysis identified PRKCE as a candidate resistance-associated dependency enriched in BTKi-tolerant tumor populations. PRKCE expression was elevated in newly diagnosed WM samples compared with healthy donor controls and was associated with inferior clinical outcome, supporting its potential role in WM progression and treatment resistance.

Functional studies demonstrated that PRKCE is required for WM cell growth and survival. PRKCE knockdown markedly reduced proliferation and increased spontaneous apoptosis in MWCL-1 cells, whereas PRKCE overexpression enhanced tumor cell growth. Cell-cycle analysis revealed that PRKCE induced G0/G1 arrest and impaired S-phase entry, indicating a critical role in regulating G1/S transition. Similar effects were observed in TMD8 cells, suggesting that PRKCE dependent signaling may extend beyond WM to other MYD88-mutant B-cell malignancies.

Importantly, PRKCE depletion enhanced sensitivity to BTK inhibition. Following ibrutinib treatment, PRKCE-deficient BCWM.1 and TMD8 cells exhibited increased apoptotic responses compared with control cells. Mechanistically, PRKCE depletion reduced phosphorylation of BTK and ERK, indicating that PRKCE maintains residual B-cell receptor (BCR)-associated signaling activity required for survival during BTK blockade.

To define downstream transcriptional programs regulated by PRKCE, RNA sequencing was performed in PRKCE-depleted BCWM.1 cells. Pathway analyses revealed significant suppression of cell-cycle-related processes, including G1/S transition, DNA replication, and chromosome segregation. Gene set enrichment analysis

demonstrated reduced MYC target, E2F targets, and G2/M checkpoint programs following PRKCE loss. Among downstream regulators, the BCR-responsive transcription factor EGR1 was significantly downregulated after PRKCE depletion and was validated by quantitative PCR. Together with reduced BTK/ERK activation, these findings identify a PRKCE-BTK/ERK–EGR1 signaling axis that sustains MYC/E2F-driven transcriptional programs and cell-cycle progression in WM.

Given that PRKCE knockdown converged on cell-cycle regulatory vulnerabilities, we evaluated whether pharmacologic targeting of cell-cycle progression could overcome BTKi resistance. The cell-cycle inhibitory compound 8b demonstrated dose-dependent cytotoxic activity in both parental and ibrutinib-resistant WM cell models, highlighting cell-cycle dependency as a potential therapeutic vulnerability after BTKi failure.

Conclusion

Our study identifies PRKCE as a previously unrecognized signaling dependency that enables WM cells to maintain survival during BTK inhibition. By sustaining BCR-ERK-EGR1 signaling and MYC/E2F-driven cell-cycle program, PRKCE promotes proliferation and BTKi tolerance. Targeting PRKCE-associated signaling or downstream cell-cycle vulnerabilities may provide new therapeutic opportunities for patients with BTKi refractory WM.

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