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Lymphomas

TARGETING CK2 DISRUPTS EPIGENETIC PLASTICITY AND SENSITIZES DIFFUSE LARGE B-CELL LYMPHOMA CELLS TO THE EZH2 INHIBITOR TAZEMETOSTAT

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Introduction: Diffuse large B-cell lymphoma (DLBCL) displays profound epigenetic deregulation driving transcriptional plasticity which sustains therapy resistance. EZH2, a key histone methyltransferase frequently altered in germinal center (GC) DLBCL, promotes aberrant H3K27me3 accumulation, rewiring chromatin states, and it is therapeutically targetable with the selective inhibitor tazemetostat. Protein kinase CK2 is a constitutively active serine/threonine kinase that controls oncogenic signaling and multiple epigenetic regulators, including DNA methyl transferase (DNMT1), histone methyltransferases (HMT), and ATP-citrate lyase (ACLY), potentially linking oncogenic signaling to chromatin organization. In DLBCL, CK2 sustains AKT and NF-κB-p65 cascades, yet its impact on epigenetic regulation remains poorly understood. We hypothesized that CK2 inhibition could constrain epigenetic flexibility and potentiate the response of epidrugs such as tazemetostat in GCB DLBCL.

Methods: CK2 expression was assessed in DLBCL cell lines versus normal B cells. Functional and epigenetic effects of CK2 inhibition were evaluated using the clinical inhibitor CX-4945 (silmitasertib) and the newly developed selective compound SGC-CK2-1 in EZH2-mutant (OCI-Ly1) and wild-type (OCI-Ly19) GCB-DLBCL cells. Viability, apoptosis, and cell-cycle distribution were determined by viability assays and flow cytometry. Western blotting of total and histone-enriched fractions was used to assess signaling and histone modification changes. A CK2 knockdown OCI-Ly1 model was generated using an IPTG-inducible shRNA system to genetically validate pharmacological inhibition. The potential synergy between CK2 inhibitors and tazemetostat was tested through combined treatment.

RESULTS

CK2 was overexpressed in DLBCL compared with normal B cells. CK2 blockade reduced cell viability, and induced apoptosis, accompanied by marked increase in repressive histone marks (H3K27me3, H3K9me) and altered histone acetylation activating markers (H3K27ac, H3k9ac), indicating a key role for this kinase in maintaining chromatin flexibility. CK2 inhibition decreased the activating phosphorylation of AKT on Ser129 and modulated DNMT1 and ACLY activity, suggesting a link between CK2 signaling, metabolic control and DNA methylation maintenance. Combination of CK2 inhibitors with tazemetostat produced a remarkable decrease in viability and enhanced apoptosis compared to single treatments.

Conclusions: .

These findings identify CK2 as a central regulator of epigenetic plasticity, linking oncogenic signaling with chromatin modifications. Combined inhibition of CK2 and EZH2 represents a promising strategy to overcome resistance and improve therapeutic outcomes in aggressive B-cell lymphomas.