XIX CONGRESSO NAZIONALE SIES2026
Firenze | 4-6 marzo 2026
Palazzo degli Affari

Lymphomas

RESISTANCE TO BET PROTEIN INHIBITORS IS ORCHESTRATED BY PROTEIN KINASE CK2 IN MANTLE CELL LYMPHOMA

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Introduction: Novel therapeutic strategies for Mantle Cell Lymphoma (MCL) are urgently needed. Bromo Extraterminal domain (BET) proteins are key epigenetic regulators that promote oncogenic transcriptional programs and signaling, including c-Myc activity and BCL2 function. Several BET protein inhibitors (BETi), such as JQ-1, INCB054329 (INCB), have shown antitumor activity, also by enhancing ibrutinib sensitivity. However, intrinsic or acquired resistance limits their efficacy.

Protein Kinase CK2, is overexpressed in MCL and other hematological malignancies, phosphorylates BRD4 and sustains pro-survival signaling (such as AKT, NF-kB, c-Myc and β--catenin). Given its potential role in the crosstalk between BCR signaling and chromatin remodeling, we hypothesize that CK2 may contribute to BETi resistance.

In the present study we established a novel JQ-1 resistant MCL cell model to dissect mechanisms of BETi resistance and tested whether CK2 inhibition by suppressing key survival pathways associated with JQ-1 resistance, could restore drug sensitivity.

Methods: MCL cell lines, as well as primary B cells from healthy donors and MCL patients, were treated with JQ-1 and INCB. Jeko-1 cells with acquired resistance to JQ-1 (JQ-1-R cells) were generated by long term exposure to escalating JQ-1 concentrations. Parental Jeko-1 cells were cultured with the same passage numbers and served as control. Proliferation, apoptosis, were analyzed by MTT, flow cytometry, detection of PARP and BCL-2 family members expression, while survival signaling by WB and RT-qPCR

Results: Most MCL cell lines and patient-derived B cells were sensitive to the BETi, though with variable susceptibility. In some cases, BETi induced compensatory activation of NF-κB and Mcl-1, suggesting pro-survival escape mechanisms. To deepen into mechanisms of JQ-1 resistance, we developed a JQ-1 resistant MCL cell line (JQ-1R) and performed its molecular characterization.JQ-1 R cells exhibited marked resistance not only to JQ-1 (IC50=243,6 µM vs IC50 wt Jeko-1=0,66 µM) but also to INCB, (IC50 INCB=580 µM vs IC50 INCB Jeko-1 wt= 0,74 µM), while retaining doxorubicin sensitivity, indicating a selective BETi resistance phenotype. Molecular profiling of JQ-1R cells revealed upregulation of CK2α/β subunits, enhanced PI3K/AKT and NFKB signaling and increased Bcl2, β-catenin, and c-Myc expression compared with the parental cell line. Importantly, CK2 inhibition with CX-4945 or SGC-CK2-1 downregulated some of these survival pathways, reduced cell viability, triggered apoptosis, and restored sensitivity to JQ-1.

Conclusions: CK2 plays a central role in orchestrating BETi resistance in MCL, likely by reprogramming transcriptional and survival compensatory pathways. Combined CK2 and BET protein inhibition represents a promising therapeutic strategy to overcome adaptive resistance in MCL.