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

XIX Congress of the Italian Society of Experimental Hematology ABSTRACT N. P085

Lymphomas

REWIRING TUMOR-DRIVEN INFLAMMATION TO RESTORE IMMUNE SURVEILLANCE IN MANTLE CELL LYMPHOMA

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Introduction: Mantle Cell Lymphoma (MCL) remains an incurable B-cell malignancy. Therapy resistance could be driven by the presence of epigenetic dysregulation and immunosuppressive tumor microenvironment (TME). Protein Kinase CK2 is a pleitropic kinase which sustains tumor cell survival via persistent PI3K/AKT, NF-κB and c-Myc activation with the potential of promoting immune evasion. c-Myc is a proto-oncogene that suppresses interferon responses, enhances IL-10 secretion, and upregulates PD-L1, collectively impairing $CD8^+$ T and NK cell cytotoxicity. Its expression could drive MCL progression. In the present study, we tested the role of CK2 in modulating c-Myc, PD-L1, IL-10 and other immunomodulating cytokines expression in MCL. By disrupting c-Myc-driven transcription and tumor released inflammatory cytokine production, CK2 inhibition could reshape the TME, reducing pathological inflammation and restoring effective antitumor immunity. This strategy might overcome immunotherapy resistance and could provide a novel therapeutic approach for MCL.

Methods: We investigated the effects of CK2 inhibitors, CX4945 and SGC-CK2-1, or CK2 gene silencing via IPTG-inducible CK2-targeting shRNAs MCL cell clones, on MCL cell survival, apoptosis, proliferation, signaling pathways, cytokines and chemokines' production. CK2 expression and survival signaling were analyzed by Western blot and RT-qPCR. The expression of 80 cytokines in the culture media from CK-2-inactivated MCL cells was evaluated using a human cytokine array detection kit and validation was performed by RT-qPCR.

Results: CK2 inactivation reduced NF-κB and PI3K/AKT pathways activation and significantly downregulates the mRNA and protein expression of c-Myc in MCL cells, accompanied by reduced IL-10 and PD-L1 expression, suggesting a potential relief of immunosuppression. Multi-cytokine profiling revealed that CK2 upregulates the activity of some pro-inflammatory cytokines such as IL-1β, TNFα, OPN and MIF and some immunosuppressive and/or anti-inflammatory cytokines and chemokines such as IL-10, CCL18, HGF, TIMP-2, highlighting its central role in immune signaling within the TME. Analysis of publicly available transcriptomic datasets (GSE46846/GSE303064) showed upregulation of pro-inflammatory gene signatures (INFγ, IL12, CXCR4, TGFβ) in patients vs normal B cells, an upregulation of *CSNK2B* in MCL relapsed vs newly diagnosed B cells, and modulation of IL10 and TNFα signaling in relapsed bone marrow MCL patients T cells vs primary diagnosed ones.

Conclusions: CK2 acts as a critical regulator of oncogenic signaling and immune modulation in MCL. Its inhibition not only suppresses tumor cell growth and survival but also attenuates pro-inflammatory signaling and cytokine release, alleviating systemic immunosuppression within the TME, potentially enhancing immune-mediated tumor clearance. These findings position CK2 as a promising therapeutic target to enhance immunotherapy efficacy in MCL.

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