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

XIX Congress of the Italian Society of Experimental Hematology ABSTRACT N. P100

Monoclonal Gammopathies & Multiple Myeloma

ENHANCED NAD$^+$ BIOSYNTHESIS AND PPP ACTIVATION DRIVE VENETOCLAX RESISTANCE IN MULTIPLE MYELOMA: THERAPEUTIC REVERSAL BY NAMPT INHIBITION

I. Traverso[1], D. Soncini[1|2], G. Giorgetti[2], S. Ravera[3], J. Ivanisevic[4], M. Garibotto[2], M. Gallo[1], F. Guolo[1|2], A. Cagnetta[2], R.M. Lemoli[1|2], M. Cea[1|2]

[1]Clinic of Hematology, Department of Internal Medicine and Medical Specialties DiMI, University of Genoa; [2]IRCCS Ospedale Policlinico San Martino; [3]Department of Experimental Medicine DIMES, University of Genoa, Italy [4]Metabolomics Unit, Faculty of Biology and Medicine, University of Lausanne, Switzerland

Introduction: Multiple myeloma (MM) is an incurable hematologic malignancy characterized by progressive metabolic reprogramming that accompanies disease evolution. During relapse, MM cells frequently acquire drug resistance, underscoring the need for new therapeutic strategies to overcome the limited efficacy of current treatments. The BCL-2 inhibitor venetoclax (Ven) shows marked activity in patients harboring the t(11;14) translocation; however, resistance frequently develops, particularly at relapse. This study aimed to identify novel metabolic vulnerabilities associated with Ven resistance by exploiting the dependence of MM cells on NAD$^+$ biosynthesis.

Methods: Drug synergy between Ven and the NAMPT inhibitor FK866 was evaluated in a panel of MM cell lines, using MTT-based viability assays. Targeted metabolomic profiling was conducted to quantify NAD$^+$ intermediates and to characterize metabolic alterations. Mitochondrial function and energy metabolism were assessed following FK866 and Ven treatment. FK866-resistant MM cells were generated through stepwise drug exposure and characterized to investigate metabolic adaptations. The clinical relevance of these findings was validated through transcriptomic analyses of MM patient datasets.

Results: Comprehensive metabolomic profiling revealed elevated nicotinamide (Nam) levels in Ven-resistant MM cells, consistent with previous findings in leukemia, suggesting that metabolic reprogramming toward enhanced NAD$^+$ biosynthesis sustains cellular fitness under Ven-induced stress. Combined treatment with Ven and FK866 elicited potent synergistic cytotoxicity across MM cell lines, irrespective of Ven-resistance status. Mechanistically, co-treatment suppressed mitochondrial respiratory complex activity, depleted intracellular ATP, and increased oxidative stress and macromolecular damage, consistent with energetic collapse. Western blot analysis revealed downregulation of glucose-6-phosphate dehydrogenase (G6PD), a key regulator of the pentose phosphate pathway (PPP) and redox homeostasis, while BCL-2 family protein levels remained unchanged, excluding mitochondrial priming as the primary mechanism of synergy. Notably, FK866-resistant MM cells displayed enhanced Ven sensitivity, distinct metabolic rewiring, and reduced G6PD expression, reinforcing the interplay between NAD$^+$ and PPP metabolism in modulating Ven response. Transcriptomic analysis of Ven-resistant patients (GSE167968) further corroborated these findings, showing elevated G6PD expression associated with inferior overall and progression-free survival.

Conclusions: This study reveals a previously unrecognized metabolic mechanism of Ven resistance in MM, driven by enhanced NAD$^+$ biosynthesis and PPP activation. These findings highlight a metabolic dependency that can be therapeutically exploited through combinatorial strategies co-targeting NAD$^+$ salvage and BCL-2 signalling to overcome resistance and improve outcomes in MM.