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

XIX Congress of the Italian Society of Experimental Hematology ABSTRACT N. P098

Monoclonal Gammopathies & Multiple Myeloma

GLUTAMINE-DEPENDENT ANAPLEROTIC REWIRING WITH PYRUVATE CARBOXYLASE DOWN-TUNING UNDERLIES PROTEASOME INHIBITORS RESISTANCE IN MULTIPLE MYELOMA

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Introduction: In multiple myeloma (MM) treated with proteasome inhibitors, cells can rewire carbon flow to survive proteotoxic stress. We generated bortezomib (BTZ)–resistant (RES) clones by chronic stepwise exposure and compared them with sensitive (SENS) counterparts in AMO and NCI-H929 cell lines.

Methods: Proteomics was performed by LC–MS/MS on an Orbitrap platform, targeted metabolomic was performed by LC-MS. RNA sequencing used the Nanopore workflow and key findings were validated by Western blot and RT-qPCR.

Results: RNA sequencing of both cell lines revealed a consistent metabolic rewiring in resistant cells. These cells exhibited broadly increased expression of respiratory-chain subunits and tricarboxylic acid cycle enzymes, indicating a heightened oxidative capacity. Concurrently, pyruvate carboxylase, the key enzyme for pyruvate-to-oxaloacetate anaplerosis, was significantly reduced. This metabolic shift was accompanied by elevated expression in glycolytic/pentose phosphate pathway and serine synthesis pathway modules. Furthermore, amino acid handling nodes were upregulated alongside MAT2A, suggesting enhanced one-carbon and S-adenosylmethionine support, consistent with an adaptive ATF4-driven integrated stress response. Moreover, heatmaps showed coordinated increases in amino-acid/ISR nodes including ASNS, SLC7A11 (xCT), SLC3A2/LAT, GLS, GLUD1, GOT1, HSPA5/XBP1, SQSTM1, and antioxidant enzymes (GCLC/NQO1/TXNRD2/HMOX1), with MAT2A suggesting one-carbon/SAM support. AMO cells showed decreased intracellular glutamine with a trend to elevated glutamate, while H929 cells displayed a significant rise in glutamate without a change in glutamine—compatible with fast Gln→Glu conversion buffered by continued uptake. Functionally, glutamine deprivation caused a sharper viability drop and lactate modulation in RES, confirming dependency. Importantly, comparing RES + glutamine vs RES in Gln-free revealed activation of SREBF/SREBP-driven programs and the cholesterol-biosynthesis superpathway, alongside reinforcement of TCA/FA β-oxidation and NRF2-mediated oxidative-stress response, indicating that lipid/sterol and redox metabolism are integral to the glutamine-supported resistant state. From UCSC Xena (MMRF-COMMPASS) we retrieved a Kaplan–Meier curve stratified by GLUD1 and GLUD2 expression. Patients with GLUD1-high tumors exhibit significantly inferior overall survival, reinforcing the importance of the glutaminolysis-driven anaplerotic program in MM progression.

Conclusions: Together, these data define an anaplerotic rerouting model, PC down-tuning limits pyruvate-derived OAA and shifts TCA fueling toward glutaminolysis. This maintains high respiratory capacity while preserving a favorable NADPH/GSH buffer and an adaptive UPR/autophagy support and one-carbon–lipid coupling that together stabilize the resistant phenotype. Targeting this metabolic vulnerability offers a promising strategy to overcome bortezomib resistance in multiple myeloma.