(PS1837) GENOMIC PROFILING UNVEILS ACTIONABLE VULNERABILITIES AND CLONAL EVOLUTION IN RELAPSED/REFRACTORY MULTIPLE MYELOMA

Topic: 13. Myeloma and other monoclonal gammopathies - Biology & translational research

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Background

Relapsed/refractory multiple myeloma (R/R MM) remains a formidable challenge, especially for patients with extramedullary disease (EMD) or resistance to immunotherapies. R/R MM undergoes complex clonal evolution under therapeutic pressure, acquiring genomic aberrations that confer aggressive phenotypes and multidrug resistance. Deciphering this genomic complexity is critical for identifying novel actionable targets and developing personalized salvage strategies.

Aims

To delineate the comprehensive genomic landscape of a real-world R/R MM cohort using ultra-deep targeted next-generation sequencing (NGS) and to evaluate the feasibility of genome-guided targeted interventions.

Methods

We retrospectively analyzed clinical and genomic data in R/R MM patients from 2024.04 to 2026.02. Bone marrow aspirates and EMD biopsies underwent customized targeted NGS (mean depth >1500x) encompassing up to 172 hematologic malignancy-related genes. Single nucleotide variants (SNVs) and small insertions/deletions (InDels) were functionally annotated. Therapeutic actionability was systematically assessed by mapping pathogenic variants to FDA/NMPA-approved targeted agents based on preclinical and clinical evidence.

Results

Ultra-deep sequencing identified a highly heterogeneous mutational landscape, revealing at least one actionable somatic alteration in a significant proportion of heavily pretreated patients. The genomic architecture driving clonal evolution was predominantly characterized by aberrations in cell cycle regulation, epigenetic modification, and PI3K/AKT/DNA damage repair (DDR) pathways: 1.Cell Cycle Dysregulation: Activating mutations in the PEST domain of *CCND3* (e.g., p.Q280X, p.P284S) and loss-of-function truncations in the tumor suppressor *CDKN2A* (e.g., p.R80X) were prevalent. These alterations stabilize Cyclin D3 and bypass the p16INK4a-Rb checkpoint, providing a strong mechanistic rationale for repurposing CDK4/6 inhibitors (e.g., palbociclib, dalpiciclib). 2.Epigenetic Reprogamming: Recurrent variants in histone modifiers, including frameshifts in CREBBP (p.E1061Rfs38) and KMT2D (p.E1207Gfs5, p.M1379Vfs*52), alongside DNMT3A missense mutations (p.P904L), were enriched in patients with EMD. These mutations drive clonal stemness but confer synthetic lethality to HDAC inhibitors (e.g., chidamide) and hypomethylating agents. 3.Signaling & DDR Defects: We identified actionable activating mutations in the PI3K/AKT pathway, such as *PIK3R1* frameshifts (p.D68Afs*7) that disrupt PTEN stability, and DDR defects including ATM truncations (p.Q2280X) conferring susceptibility to PARP inhibitors. Furthermore, NOTCH1 truncations (p.P2514Rfs*4) and *SAMHD1* variants (p.R366H) were observed in aggressive clones. Clinically, identifying these intrinsic vulnerabilities enabled the deployment of genome-guided off-label targeted combinations as salvage or bridging therapies prior to cellular immunotherapy.

Summary/Conclusion

Ultra-deep targeted NGS unveils a complex, actionable molecular architecture in R/R MM, particularly in cases with EMD or aggressive clonal evolution. The enrichment of specific cell cycle (*CCND3/CDKN2A*), epigenetic (*CREBBP/KMT2D/DNMT3A*), and kinase (*PIK3R1*) mutations presents profound therapeutic opportunities. Integrating genome-driven precision medicine—such as repurposing CDK4/6, HDAC, and PI3K/mTOR inhibitors—offers a promising, mechanistically sound salvage strategy for R/R MM patients who have exhausted standard options.

Pathway	Key Mutated Genes	Representative Variants	Potential Targeted Agents
Cell Cycle	CCND3, CDKN2A	p.Q280X, p.P284S, p.R80X	CDK4/6 inhibitors
Epigenetic	CREBBP, KMT2D, DNMT3A	p.E1061Rfs*38, p.E1207Gfs*5, p.P904L	HDAC inhibitors, HMAs
PI3K/AKT	PIK3R1	p.D68Afs*7	PI3K/mTOR inhibitors
DNA Repair	ATM	p.Q2280X	PARP inhibitors

Actionable Genomic Alterations and Genome-Guided Strategies