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Monoclonal Gammopathies & Multiple Myeloma

P53 ISOFORM DIVERSITY IN MULTIPLE MYELOMA: UNEXPLORED RISK FACTOR BEYOND TP53 MUTATION AND DEL(17P)

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Introduction: In multiple myeloma (MM), TP53 abnormalities (deletions/mutations) confer high-risk disease. Beyond full-length p53 (p53FL), alternative isoforms modulate p53 activity and cellular stress responses, but their expression patterns and clinical impact remain largely unexplored. Defining isoform-specific biology may refine risk stratification and enable personalized therapy.

Aim: To enhance MM risk stratification by integrating p53 isoforms expression profiles, improving prognostic accuracy, identify novel molecular subgroups, and ultimately supporting tailored therapeutic strategies.

Patients and Methods: RNA-sequencing data from 659 newly diagnosed MM patients (pts) (CoMMpass) were analysed for major p53 isoforms. Expression levels were classified as absent, low, or high using median-based cut-offs. Associations with genomic features, treatment response and survival outcomes were evaluated. Isoform expression was combined with cytogenetic risk to define novel prognostic categories.

Results: p53FL and p53β were widely expressed (95% and 99%), while p53γ, Δ40p53α and Δ133p53α/β showed heterogeneous patterns. High p53FL often co-occurred with high p53β and Δ133p53α, while absence of Δ133p53β was enriched in pts with high p53FL/p53β, suggesting functional interactions among isoforms. Del(17p) was detected in 10.8% of pts and associated with lower p53FL/p53β expression ($p<0.0001$); pts expressing Δ133p53β did not carry del(17p) ($p<0.0001$). Absence of p53FL (4.9%) correlated with elevated LDH, poorer treatment response, and markedly reduced progression-free survival (PFS: 7.0 vs 32.8 vs 20.6 months (mos)) and overall survival (OS: 7.0 vs 60.3 vs 36.7 mos) for absent, high, and low expression, respectively ($p<0.001$). p53β expression correlated with favorable biological features, while Δ133p53β identified a small subset with poor prognosis ($p<0.001$). Integrating isoform profile with key cytogenetic abnormalities stratified pts into favorable, poor, and intermediate risk groups. Notably, poor-risk pts had significantly higher hazards for PFS (HR 2.74, 95% CI 1.50–4.99, $p=0.000987$) and OS (HR 3.79, 95% CI 1.91–7.51, $p<0.001$) compared with favorable-risk pts. Combined with ISS, poor-risk pts with ISS III had markedly shorter PFS (median 11.5 mos) and OS (median 21.1 mos) than favorable-risk pts (PFS 46–50 mos, OS 102 mos). Isoform-based risk retained independent significance in multivariate models (interaction $p=0.002$), improving the prognostic accuracy.

Conclusion: p53 isoform profiling captures MM heterogeneity and identifies high-risk pts beyond conventional TP53 assessment. An isoform-based risk classifier robustly stratifies PFS and OS, particularly when combined with ISS, supporting its potential as a prognostic tool for personalized management. Prospective validation is warranted prior to clinical implementation.

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