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Monoclonal Gammopathies & Multiple Myeloma

EXPLORING THE TRANSCRIPTIONAL PROFILE OF DIS3 CAN UNRAVEL NEW TARGETING STRATEGIES IN MULTIPLE MYELOMA

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Introduction: Multiple myeloma (MM) is a rare hematologic malignancy marked by neoplastic transformation of plasma cells (PCs) that are characterized by deep genomic instability. Karyotype abnormalities are considered early events in MM, whereas gene mutations arise later and are related to disease progression. Mutations of DIS3 were found in 10% of MM patients and were preferentially localized within the major ribonuclease (RNB) domain affecting its catalytic activity. In addition, del(13q) found in 40% of MM cases, impact the expression of DIS3. This gene encodes a highly conserved 3′–5′ exoribonuclease associated with the RNA-exosome complex essential for RNA turnover. Here, we characterized the transcriptional landscape induced by DIS3 silencing in an MM cell line and exploited the resultant signature to identify putative synergistic compounds.

Methods: DIS3 silencing was performed using LNA-gapmeR designed for gymnosis. Transcriptome profiling by bulk RNA-seq of DIS3-silenced NCI-H929 cells versus gapmeR scrambled as controls was carried out on an Illumina NextSeq 500; DESeq2 pipeline was used for differentially expressed genes analysis. Immunofluorescence experiments were performed using anti α-Tubulin 488-conjugated for mitosis and S9.6 antibody for R-loop detection.

Results: Differential expression analysis of RNA-seq identified 809 significantly deregulated genes (FDR<0.05), particularly 492 and 317 genes were found upregulated and downregulated respectively. GO bioprocess analysis of downregulated genes were enriched in microtubule and kinetochore assembly, promoting regulatory role of DIS3 in mitotic spindle organization. Interestingly, upregulated genes were predominantly associated with antiviral immune response and interferon-mediated signaling, a pattern possibly due to RNA accumulation. Additionally, immunofluorescence staining of DIS3 silenced cells showed increased R-Loop formation. To identify synergistic agents consistent with $DIS3^{KD}$ signature, the CMap query analysis revealed a strong association with microtubule-targeting inhibitors. Filanesib (ARRY-520) is a selective kinesin inhibitor of EG5/KIF11 that is fundamental mitotic kinesin necessary for spindle orientation. It has been previously studied for MM therapy—either as monotherapy or in combination—within phase II clinical trials. Filanesib treatment negatively affected cell viability in MM cell lines harboring del(13q) compared to bi-allelic WT counterparts. Furthermore, co-treatment with Filanesib and DIS3 LNA-gapmer produced a synergistic cytostatic response.

Conclusions: Our rusults suggest that $DIS3^{KD}$ perturbs mitotic spindle dynamics and fosters genomic instability in MM, consistent with prior evidence that DIS3 depletion increases G0/G1-phase accumulation and compromises centrosome formation. In addition, the synergy observed with a microtubule-targeting agent could encourage future investigation to improve MM treatment strategies.