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Monoclonal Gammopathies & Multiple Myeloma

DISSECTION OF NEAT1'S ROLE IN TRANSCRIPTIONAL REGULATION REVEALS ACTIONABLE TARGETS IN HIGH-RISK MULTIPLE MYELOMA

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Introduction: LncRNAs emerged as a key element of genome regulation, driving multiple myeloma (MM) progression and therapy resistance. Among them, NEAT1 has been described as overexpressed in MM patients, promoting malignant PC proliferation. Besides its conventional function in the assembly of paraspeckles, we recently demonstrated that NEAT1 is directly involved in transcriptional control. In this study, we deepen our understanding of NEAT1's mechanistic function in shaping the activity of transcriptional bodies, providing the rationale for targeted therapeutic intervention. Methods: We used an RNA-seq approach in NEAT1 KD and in CRISPRa NEAT1 overexpressing AMO-1 cell line to derive a NEAT1 transcriptomic signature. Unsupervised clustering analysis in the CoMMpass dataset was used to validate the clinical relevance of the NEAT1 gene program. Computational approaches were used to predict a list of transcriptional regulators of NEAT1's signature. RNA immunoprecipitation (RIP) and RNA-FISH combined with immunofluorescence (IF) were used to confirm the in silico prediction in AMO-1 and NCI-H929 cell lines. Chromatin immunoprecipitation (ChIP) was employed to validate the involvement of NEAT1 in the transcriptional apparatus. High-throughput (HT) drug screening in NEAT1 KD cells was used to identify small compounds that interfere with NEAT1-dependent transcriptional activity. Rescue experiments were performed using NEAT1 overexpressing cells. Results: Transcriptomic analysis in NEAT1 KD and in NEAT1 overexpressing AMO-1 cell line revealed 378 NEAT1 targets. Unsupervised clustering analysis based on their expression segregated CoMMpass patients into two distinct groups, displaying high or low NEAT1 transcriptional activity. The cluster with the high NEAT1 transcriptional program showed reduced survival and was enriched in high-risk cytogenetic lesions, including 1q gain/amp and del(17)p. Noticeably, computational analysis predicted FOXM1 and CDK9 as upstream regulators of the NEAT1 program, both components MMB:FOXM1 transcriptional apparatus, which controls the expression of G2/M genes. Consistently, we highlighted that 60% of NEAT1 target genes harbor a Cell cycle homology region (CHR) motif, recognized by MMB:FOXM1 complex. In vitro molecular validation confirmed co-localization of NEAT1 and FOXM1 condensates in MM cells, and direct binding of NEAT1--FOXM1/NEAT1-CDK9. Additionally, we demonstrated that NEAT1 KD results in a reduced occupancy of FOXM1 at the promoters of CHR genes. HT drug screening revealed a synthetic lethal interaction between NEAT1 depletion and CDK9 inhibition, whereas its overexpression confers resistance to CDK9 blockade, confirming the interplay between NEAT1-CDK9 to sustain the mitotic gene program. Conclusion: These findings demonstrate that NEAT1 coordinates the expression of mitotic genes through the interaction with FOXM1 and CDK9, providing a mechanistic rationale for targeted interventions in high-risk patients.