MINNELIDE, A PROMISING COMPOUND FOR THE TREATMENT OF HIGH-RISK MEDULLOBLASTOMA

MDB-107. MINNELIDE, A PROMISING COMPOUND FOR THE TREATMENT OF HIGH-RISK MEDULLOBLASTOMA

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Serge Stefanyda

ANTIBODY DELIVERY TO HIGH-RISK MEDULLOBLASTOMAS

TUMOR BARRIER DISRUPTION FOR AUGMENTATION OF THERAPY, SUGGESTING ITS POTENTIAL REPURPOSING FOR TREATING MYC-DRIVEN G3 MODELS. FURTHERMORE, MINNELIDE ENHANCED THE EFFICACY OF ADJUVANT CHEMOTHERAPY

MINNELIDE, AN ANALOG OF THE NATURAL PRODUCT TRIPOLIDE, EXHIBITS POTENT ANTITUMOR ACTIVITY IN PRECLINICAL AND EARLY CLINICAL SETTINGS.

PROGNOSIS FOR THESE PATIENTS UNDERSCORES THE URGENT NEED FOR ADVANCING THERAPEUTIC APPROACHES. MINNELIDE, AN ANALOG OF THE NATURAL PRODUCT TRIPOLIDE, EXHIBITS POTENT ANTITUMOR ACTIVITY IN PRECLINICAL AND EARLY CLINICAL SETTINGS.

CONCLUSION: SPATIAL TRANSCRIPTOMICS ENABLES NEW INSIGHT INTO THE HETEROGENEITY OF THE MEDULLOBLASTOMA TME. NOTABLY, OUR ANALYSIS ELUCIDATES THE SPATIAL ASSOCIATION OF TAMs AND TAAs WITH PROLIFERATING TUMOR CELLS AND THE MECHANISM OF TUMOR PROGRESSION AND SPREAD.

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BACKGROUND: Medulloblastoma (MB), a childhood brain tumor, emerges typically between 6-8 years, originating from cerebellar neuronal stem cells. Recurrent genetic alterations, notably MYC amplifications, are associated with poor therapy response. Subgrouped as WNT-MB, SHH-MB, Group 3 MB, and Group 4 MB, Group 3 MB is characterized by high-level MYC amplification in approximately 17% of cases. Patients with Group 3 MB and MYC activation present distinct transcriptional and proteomic signatures, including elevated levels of ribosomal proteins and ribosome assembly proteins.

METHODS: We conducted a comprehensive analysis of RNA-seq and Ribo-seq in human neural stem cells (H9 NSCs) with amplified MYC expression. H9-NSCs were cultured in tumor stem media and transduced with lentivirus for either GFP control or MYC cDNA. RNA and ribosome-protected fragments were isolated from cell lysates for RNA-seq and Ribo-seq in biological triplicates. Ribo-seq data was analyzed using ORFquant for coding sequence quantification and deltaTE for translational efficiency. RESULTS: Overexpressing MYC in H9-NSCs led to significant differential expression of 4194 genes (p adj < 0.05) using RNA-seq and 2860 genes (p adj < 0.05) using Ribo-seq. While RNA-seq and Ribo-seq exhibited high correlation for most genes, we identified 364 differentially translated genes (p adj < 0.05) upon MYC overexpression. Genes regulated solely at the translational level were enriched for functions in cytoplasmic translation initiation, viral translation, and response to interleukin-4. Key genes highly regulated at the Ribo-seq level included CCND1, YBX1, and EEF2.

Validating with proteomics data from the CPTAC medulloblastoma tissue set confirmed protein-specific upregulation of these targets in MYC-driven Group 3 medulloblastomas. CONCLUSIONS: MYC overexpression revealed distinct behaviors in differentially expressed genes, either regulated at the level of translation alone, correlated with transcription, or independent of transcription. We anticipate that our findings will contribute to a refined understanding of the molecular landscape of MB, particularly in the context of Group 3 MB.

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MDB-109. CHARACTERIZING DISTINCT SIGNATURES OF RNA TRANSLATIONAL REGULATION UPON MYC OVEREXPRESSION IN H9 NEURAL STEM CELLS

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