RBM39 as a therapeutic target in Nasopharyngeal Cancer

Prachi Amuley1 1Nanyang Technological University, Singapore, Singapore

Background: Aberrant alternative splicing is a hallmark of cancer, driven in part by dysregulated RNA-binding proteins. RBM39, an essential splicing factor and transcriptional coactivator, is increasingly implicated in tumour biology and is recognized as the cellular target of aryl sulphonamide molecular glue degraders such as Indisulam. Despite its established dependency in haematological malignancies, the full extent of RBM39-regulated splicing events that drive Nasopharyngeal Carcinoma (NPC) tumour progression and the therapeutic potential of targeting this axis remain poorly characterized. Method: To define RBM39's oncogenic splicing program in NPC, we integrate: RBM39 depletion via siRNA based Knockdown and targeted protein degradation using aryl sulphonamide compounds; transcriptome-wide RNA sequencing and differential splicing analysis to map RBM39-regulated splicing events; functional validation of key splicing targets using splice-switching antisense oligonucleotides; in in vitro cell line based models to evaluate NPC-cell dependency and therapeutic vulnerability associated with RBM39 loss. Results: Preliminary analyses indicate that RBM39 coordinates a pro-tumourigenic splicing program affecting pathways critical for cell survival and proliferation, with disruption of this splicing program impairing tumour cell viability. Importantly, NPC cells exhibit marked sensitivity to the RBM39 degraders Indisulam and Tasisulam, and combinatorial treatment strategies further enhance the efficacy of these drugs, suggesting a therapeutic opportunity for RBM39-directed intervention in NPC. Ongoing experiments aim to compare the RBM39-dependent splicing program across different solid tumours, identify common cancer-essential splicing targets, and define determinants of therapeutic sensitivity. Conclusion: This work establishes RBM39 as a reliable therapeutic target in NPC and provides a mechanistic rationale for exploiting splicing factor dependency in this cancer type. Our findings will support development of RNA splicing-directed therapies and expand the clinical applicability of RBM39-targeting strategies in NPC.