Coordinated Splicing of Regulatory Detained Introns within Oncogenic Transcripts Creates an Exploitable Vulnerability in Malignant Glioma

Highlights

- DI splicing is a regulated pathway promoting proliferation gene expression
- GBMs assume control of the DI pathway, creating an exploitable vulnerability
- PRMT5 inhibition induces DI inclusion and yields potent anti-tumor activity
- CLNS1A/RIOK1 ratio is a predictive biomarker for PRMT5 inhibitor sensitivity

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In Brief

Braun et al. show that glioblastoma is selectively sensitive to the inhibition of PRMT5 and identify a predictive biomarker for this sensitivity. PRMT5 inhibition primarily disrupts the removal of detained introns, which results in the reduction of functional transcripts of mainly proliferation-associated genes.
Coordinated Splicing of Regulatory Detained Introns within Oncogenic Transcripts Creates an Exploitable Vulnerability in Malignant Glioma

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http://dx.doi.org/10.1016/j.ccell.2017.08.018

SUMMARY

Glioblastoma (GBM) is a devastating malignancy with few therapeutic options. We identify PRMT5 in an in vivo GBM shRNA screen and show that PRMT5 knockdown or inhibition potently suppresses in vivo GBM tumors, including patient-derived xenografts. Pathway analysis implicates splicing in cellular PRMT5 dependency, and we identify a biomarker that predicts sensitivity to PRMT5 inhibition. We find that PRMT5 deficiency primarily disrupts the removal of detained introns (DIs). This impaired DI splicing affects proliferation genes, whose downregulation coincides with cell cycle defects, senescence and/or apoptosis. We further show that DI programs are evolutionarily conserved and operate during neurogenesis, suggesting that they represent a physiological regulatory mechanism. Collectively, these findings reveal a PRMT5-regulated DI-splicing program as an exploitable cancer vulnerability.

INTRODUCTION

Glioblastoma (GBM) is a highly malignant brain tumor with a grim clinical prognosis despite aggressive and multi-modal treatment regimens (Stupp et al., 2005). With few exceptions, there is a dearth of targeted therapeutics to treat this disease (Lau et al., 2014). Moreover, there is a lack of well-defined GBM dependencies that represent possible therapeutic targets. In vivo loss-of-function screens offer an unbiased method to identify cellular processes that represent key vulnerabilities for cancer cells. These screens are particularly useful in identifying cancer dependencies that are not induced by mutation and, consequently, not revealed by tumor genome sequencing efforts (Gargiulo et al., 2014). However, high-throughput genetic approaches are challenging in GBM where the heterogeneity and consequent differential growth rates of patient-derived xenograft (PDX) tumors causes high experimental noise.

Recent publications have suggested that aberrant RNA splicing is essential to the development and progression of certain malignancies (Dvinge et al., 2016). A putative regulator...
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