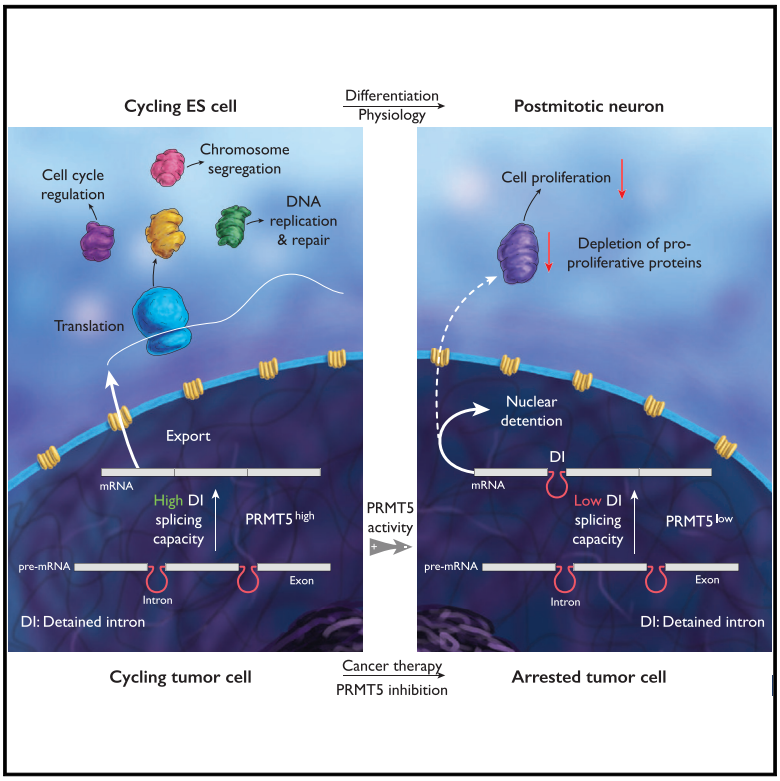
Article

Cancer Cell

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

Graphical Abstract



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.

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

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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

Significance

PRMT5 inhibitors are an emerging class of targeted cancer therapeutics. However, even highly promising molecularly oriented agents have frequently yielded disappointing results in clinical trials due to a lack of predictive biomarkers enabling pre-selection of patients most likely to respond to therapy. Here, we overcome this constraint by establishing that tumor cells sensitive to the lead PRMT5 inhibitor EPZ015666 are "addicted" to a specific form of splicing, detained introns. Sensitive cells exhibit an altered expression ratio of two PRMT5 co-factors, which skews PRMT5 methylation activity toward core components of the spliceosome and acts as a predictive biomarker for EPZ015666 sensitivity. We thus define a broad and targetable splicing program, which may be exploitable for therapy far beyond PRMT5 inhibition.