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Exploring Splicing Dysregulation in Glioblastoma and Its Modulation through RNA-Targeting Strategies

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Glioblastoma (GB) is the most frequent and lethal primary brain tumor. Despite the availability of standard treatment for this type of tumor, which consists of surgical resection followed by radiotherapy and chemotherapy, GB remains resistant to treatment and recurrence is inevitable. GB exhibits high inter- and intra-tumor heterogeneity, which poses a challenge for the development of effective therapies.

We have studied RNA mis-splicing (AS) and its impact in GB to better understand the biological mechanisms underlying GB with the final objective of developing RNA therapies as a future therapeutic approach. Bioinformatics analysis of RNA-seq data from the Chinese Glioma Genome Atlas (CGGA) (http://www.cgga.org.cn) identified hundreds of differentially expressed splicing events. Consistent with previous studies, our analysis reveals a mutually exclusive exon (MXE) in the PKM gene, encoding Pyruvate kinase M1/M2, which is differentially regulated in the GB samples of CGGA database. Next, we have validated PKM AS event in additional patient-derived GB tumor samples and Glioma Stem Cells (GSCs) obtained from surgical aspirates of patients who undergo tumor resection in Donostia University Hospital. Finally, we hypothesize that correcting RNA missplicing in GB could have therapeutic benefits for these patients. To this end, we employ RNA-targeting approaches such as antisense oligonucleotides (ASOs) and CRISPR-dCas13 system. In vitro, we have studied PKM1/2 splicing modification and its impact on cell proliferation and self-renewal ability.

In conclusion, our preliminary results indicate that PKM mis-splicing might have a key role in GB, and that RNA splicing switch may serve as a future therapeutic strategy against GB.