DEPARTMENT OF BIOLOGICAL SCIENCES

PHD THESIS DEFENSE

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Study of DNA methylation-mediated regulation of *PKM* splicing in breast cancer

The cancer cells thrive on glucose by converting it to lactate at the end of glycolysis. The phenomenon is known as aerobic glycolysis or Warburg effect (1) and promotes growth of the cancer cells (2-3). The alternative spliced isoform Pyruvate kinase M2 (PKM2) contributes to the Warburg effect by promoting aerobic glycolysis whereas PKM1 isoform promotes oxidative phosphorylation (4). The *PKM* gene contains two mutually exclusive exons, exon 9 and 10 which are alternatively included in the final transcript to give rise to *PKM1* and *PKM2* isoform respectively (5). In this study, we report that the intragenic DNA methylation mediated binding of BORIS (Brother of regulator of imprinted sites) at the alternative exon of *Pyruvate Kinase* (*PKM*) is associated with cancer-specific splicing that promotes Warburg effect and breast cancer progression. Interestingly, inhibition of DNA methylation or BORIS depletion or CRISPR/Cas9-mediated deletion of BORIS binding site leads to splicing switch from cancer specific *PKM2* to normal *PKM1* isoform. This results in the reversal of Warburg effect and inhibition of breast cancer cell growth, which may serve as a useful approach to inhibit the growth of breast cancer cells. Importantly, our results show that in addition to *PKM* splicing, BORIS also regulates alternative splicing of several genes in a DNA methylation-dependent manner. Our findings highlight the role of intragenic DNA methylation and DNA binding protein, BORIS in cancer-specific splicing and its role in tumorigenesis.

References:

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