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A novel post-transcriptional mechanism for inhibiting the expression of PTEN in breast cancer

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Splicing of introns in the pre-mRNA is an important post-transcriptional step, as the final protein product depends on the sequence of the mature mRNA. Thus, normally this splicing function is tightly regulated. A subset of genes contain a specific type of intron, called minor introns, present in highly conserved genes, including tumor suppressors and oncogenes. We have previously found that a subset of these introns is dysregulated in breast cancer. The regulation of minor introns in breast cancer is not fully studied, so to further understand this, we analyzed the expression of minor intron containing genes in 1200 breast cancer samples. Analysis of RNA-seq data identified several minor intron-containing genes whose expression seems to be differentially regulated in breast cancer. Next, we used Antisense Morpholino Oligonucleotides (AMOs) to inhibit the splicing of specific introns in a breast cancer cell line (MDAMB-231) to check whether the inhibition of minor intron splicing affects the behaviour of these cells. For this, we utilized RT-PCR and western blot to check transcript and protein levels, as well as proliferation and motility assays to check for cancer cell behavior. Finally, using computational analysis, a database of RNA-Binding Proteins (RBPs) that interact and potentially affect the aberrant splicing of specific minor introns in breast cancer was curated. Our results show that the pre-mRNA of the tumor suppressor gene PTEN, phosphatase and tensin homolog, contains a minor intron and is dysregulated. The AMO transfection that inhibited minor intron splicing of PTEN showed increased unspliced mRNA transcripts and consequently indications of increased proliferation and migration. A list of RBPs that bind to the PTEN minor intron was compiled. In conclusion, PTEN, a gene commonly dysregulated in cancers, contains a minor intron, and when its splicing is inhibited, cancer cells behave more aggressively, suggesting a novel mechanism for down regulating tumor suppressors, such as PTEN, in breast cancer by altering the splicing of their minor intron. Thus, understanding how the cells alter minor intron splicing of PTEN could be a therapeutic target in breast cancer.

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