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## MAPK14 splicing as a novel biomarker in breast cancer

**Nourhan ElKhatib, Ettaib El Marabti and Ihab Younis**
Carnegie Mellon University, Qatar

Splicing in eukaryotes is the removal of intervening sequences, called introns, from the pre-mRNA. The majority of introns are spliced out by small Ribo Nucleo Proteins (snRNPs) which are part of the spliceosomes. A small number of introns called 'minor' introns have been identified, and they comprise less than 0.4% of all introns in humans. These introns have unique sequences that are recognized by U11, U12, U4atac,U5 and U6atac snRNPs, which are much less abundant than the 'major' spliceosomes. Such specialized introns have been shown to provide a unique opportunity for regulation of the genes that contain them. Minor intron-containing genes play key roles in cell cycle, transformation, DNA damage repair and signal transduction. Misregulation of any of these functions is associated with diseases, including cancer. Breast cancer is one of the leading causes of cancer mortality in females worldwide. Qatar's incidence rate of breast cancer is dramatically increasing. Using RNA seq data of 1200 breast cancer samples, we have previously shown that splicing of some minor intron-containing genes, including MAPK14, is dysregulated. MAPK14 gene encodes p38MAPK protein, which is a stress-induced mitogen-activated protein kinase that functions in relaying different extracellular stimuli and plays a key role in metastasis, a hallmark of cancer. To identify the molecular mechanisms that regulate the expression of MAPK14 post-transcriptionally, specifically the splicing of introns in breast cancer cells, we used antisense morpholino oligonucleotides (AMOs) to regulate MAPK14's minor intron splicing. We then assessed the effect on breast cancer cell behavior, using MTT and migration assays. We also used RNA-seq data and computational analysis to curate a database of RNA binding proteins that could potentially impact minor intron splicing in breast cancer. In conclusion, we identified MAPK14's minor intron as a novel biomarker that is regulated in breast cancer cells. Our data also sheds a new light on a positive role, yet unknown mechanism in carcinogenesis.

nelkhati@andrew.cmu.edu

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