A Potential Pancreatic Cancer Treatment in Pre-mRNA Splicing Inhibition: An Innovative Approach by Identifying Vulnerabilities in Pancreatic Cancer Cells Using Biflavonoid Isoginkgetin and Pladienolide B

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This research project identifies previously unknown vulnerabilities in pancreatic cancer cells that can be used to target cancer treatment. This research manipulates a step in the central dogma process (the biological process by which genes are expressed to synthesize proteins). The function of an essential protein (spliceosome) is inhibited by treatment by splicing inhibitors biflavonoid-isoginkgetin and pladienolide-B. This causes pancreatic cancer cells to express versions of genes (isoforms) that weaken the cells by inhibiting splicing (an essential process that aids in the synthesis of final mRNA). These newly discovered weaknesses, cancer-specific differential isoform expressions, are places to target for treatment. Splicing was inhibited using two inhibitors: pladienolide-B and biflavonoid-isoginkgetin. Three concentrations of each inhibitor were applied on four different cell types: aggressive and less aggressive pancreatic cancer cells (test), and healthy pancreatic and kidney cells (control and general control). The expression of eight different genes and their isoforms were tested using reverse transcription polymerase chain reaction. This resulted in 256 isoform expression data points. Additionally, the levels of the DBR1 protein (clean-up protein in the splicing process) were tested in all four cell types using Western Blotting. This experiment discovered five previously unknown vulnerabilities in pancreatic cancer cells. These weaknesses and missing defense mechanisms are targets for future treatment research. They were identified through differential isoform expression and DBR1 protein expression in cancer cells compared to healthy cells. Future research will utilize AI to expand the search of vulnerabilities into several thousand genes.

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