ROLE OF APLP2 IN KINASE SIGNALING IN PANCREATIC CANCER

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Pancreatic cancer is well-known for its aggressive nature and ability to metastasize, often leading to late-stage diagnosis. This study focuses on the amyloid precursor-like protein 2 (APLP2), a member of the amyloid precursor protein (APP) family that is upregulated in various cancers, including pancreatic cancer, where it promotes cell migration, invasion, and metastasis. Previous studies have indicated that reduction of APLP2 leads to decreased activation of the c-Jun N-terminal kinase (JNK) signaling pathway, but its broader effects on kinase signaling pathways in human pancreatic cancer remain unclear. This research investigates how APLP2 expression influences JNK and other kinase signaling pathways in pancreatic cancer cells. We hypothesize that reducing APLP2 levels in S2-013 human pancreatic cancer cells alters JNK activation and other key signaling pathways.

To test this hypothesis, we performed siRNA-mediated APLP2 knockdown in S2-013 cells, confirming knockdown efficiency via Western blot. Western blot analysis also assessed total JNK expression, which remained unchanged following APLP2 knockdown. Additionally, a Human Phospho-Kinase Array was used to determine the relative phosphorylation levels of 37 kinase sites in APLP2 knockdown and scramble control samples. The array identified key alterations in kinase signaling, including a pronounced increase in phosphorylation of the proline-rich Akt substrate of 40 kDa (PRAS40) and decreases in phosphorylation of CREB, ERK1/2, and JNK 1/2/3, suggesting APLP2 influences multiple signaling pathways in pancreatic cancer cells. Qiagen Ingenuity Pathway Analysis (IPA) identified three major signaling pathways most affected by APLP2 knockdown: (1) MAPK targets/nuclear events mediated by MAP kinases, (2) G-protein coupled receptor (GPCR) signaling, and (3) FAK signaling.

Together, these findings suggest that APLP2 regulates key signaling pathways driving pancreatic cancer progression and provides insights into the molecular mechanisms by which APLP2 contributes to pancreatic cancer's aggressive nature. Future studies will assess whether JNK inhibition modulates the effects of APLP2 knockdown on cell migration in S2-013 cells.

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