and soft agar colony growth formation were significantly inhibited by Galunisertib signalling and AXL could converge on p38 MAPK activation. In this respect, combined inhibition of AXL in colorectal cancer (CRC). We have previously demonstrated that targeting AXL mediated cell migration, invasion and angiogenesis. We assessed the expression and activation of TGF-β p38 MAPK proteins. However, in contrast to parental LOVO cells, no increase in p38 MAPK was found in LOVO shAXL clones, upon TGF-β stimulating HCT116 and LOVO epithelial to mesenchymal transition, invasiveness, angiogenesis and immune modulation. We have silencing drives cancer cells from aerobic glycolysis to mitochondrial dependent metabolism. A deeper knowledge of its downstream molecular pathways might give the rationale for individual pharmacological inhibition and combination with other therapies, thus improving the efficacy of the available treatments.

**Background:** AKT/PKB is a protein kinase that plays a key role in cancer, as different oncogenic pathways on it. Three isoforms with a similar structure have been described: AKT1/PKBα, AKT2/PKBβ and AKT3/PKBγ. Although there is evidence that each isoform yields specific functions, which may vary depending on the cell type, the data available about downstream pathways is scarce. Our project evaluates the consequences of the individual inhibition of each isoform in pancreatic adenocarcinoma cells.

**Methods:** We have individually silenced each AKT isoform short hairpin RNAs (shRNAs) delivered by lentiviral transduction. Cells transduced with an unspecific shRNA were used as controls. Then, high-throughput quantitative proteomic analyses were performed to evaluate the differential signaling routes altered by silencing of each AKT isoform. Lastly, Western Blot and proliferation, apoptosis and chemosensitivity experiments have been completed.

**Results:** 3930 proteins were identified with a false discovery rate (FDR) lower than 1%. Proteome pairwise comparisons were performed with the cells lines. The specific silencing of each isoform lead to differential protein expression profiles, although KEGG pathway analysis tools revealed that many of the pathways altered were common. Individual silencing of any AKT isoform caused an inhibition of glycolysis and a subsequent increase of mitochondrial activity, as seen by fluorescent mitochondrial staining. AKT silencing increased gemcitabine sensitivity for all isoforms. AKT1 and AKT2 increased 5-FU sensitivity, while AKT3 had a comparable value. Western Blot demonstrated an increase in mTOR expression after AKT1 and AKT2 silencing. p-EIF4B expression was decreased after AKT2 and AKT3 silencing. No differences were observed in ERK expression.

**Conclusions:** AKT isoforms have specific functions in pancreatic adenocarcinoma. Its silencing drives cancer cells from aerobic glycolysis to mitochondrial dependent metabolism. A deeper knowledge of its downstream molecular pathways might give the rationale for individual pharmacological inhibition and combination with other therapies, thus improving the efficacy of the available treatments.

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