Stony Brook University
The Graduate School

Doctoral Defense Announcement

Abstract

The role of serine/threonine kinase AKT1/2/3 in pancreatic cancer progression

By

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Serine/threonine kinase AKT plays a well-established role in cell metabolism and growth, but AKT inhibitors remain largely unproductive in treating pancreatic cancer. To understand this discrepancy, using the most advanced proteolysis-targeting chimeras (PROTACs) and CRISPR-Cas 9-mediated genome editing, we discover that all three isoforms of AKT, i.e. AKT1, AKT2, and AKT3, play a nonredundant role in promoting pancreatic tumor in vitro and in vivo growth. We demonstrate that insulin-like growth factor 1 (IGF1), but not epidermal growth factor (EGF), promotes pancreatic tumor cell growth in an AKT1/2/3-dependent manner. RNA-seq shows that *Akt1/2/3* loss results in dramatic transcriptomic changes, and suggests that AKT1/2/3's regulation of tumor growth is at least in part mediated by reduced cholesterol synthesis, plasma membrane incorporation, and consequent insulin-like growth factor receptor 1 (IGF1R) insensitivity. Overall, we validate that AKT1/2/3 is an effective therapeutic target by protein degradation instead of traditional kinase inhibition in pancreatic tumors, and propose that to degrade AKT1/2/3 may have a synergistic efficacy when combined with chemotherapies like gemcitabine.

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