Starving Cancer from the Inside and Outside: Nutrient Stress in Combination with Autophagy Inhibition Kills Pancreatic Ductal Adenocarcinoma

Pancreatic ductal adenocarcinoma (PDAC) is one of the most fatal cancers worldwide, with a 5-year survival rate of less than 5%. Thus, novel strategies for prevention and treatment of this disease are urgently needed. Most PDAC tumors acquire mutations resulting in permanent activation of the GTPase KRAS, which promotes mitogen activated protein kinase (MAPK) signaling and tumor development. Notably, KRAS-driven PDACs often exhibit heightened dependence on autophagy, the process by which cells degrade internal components to mobilize energy stores. Autophagy is essential for tumorigenic growth, especially under nutrient deplete conditions. While the decreased levels of growth factors and cytokines associated with exogenous nutrient deprivation slow tumor growth, the induction of autophagy enables continued tumor formation. Therefore, systemic dietary nutrient stress concurrent with autophagy inhibition may synergize to drive metabolic dysfunction and more effectively stunt tumor progression. To determine how PDACs depend on autophagy under conditions of nutrient stress, we first created an autophagy-deficient PDAC cell line. Using CRISPR/Cas9 technology, we deleted autophagy related 5 (Atg5), a key gene in autophagic induction, in a murine-derived KRAS-mutant PDAC cell line (Panc-02). Upon orthotopic, intrapancreatic injection in a syngeneic mouse model, the complete loss of autophagy in Atg5-/− cells generated tumors of comparable size and incidence relative to control, Atg5+/+ cells. Additionally, no differences in growth were observed in vitro under standard growth conditions or in combination with nutrient stress, indicating adaptation to permanent autophagy deficiency. However, when combined with nutrient stress, the application of chloroquine, a pharmaceutical inhibitor of autophagy, elicited a compounding effect on cell proliferation in both murine- and human-derived PDAC (Atg5+/+) cells, in vitro. Thus, our findings suggest that limiting nutrient availability in combination with autophagy inhibition could provide an effective adjuvant therapy to slow the progression of PDAC.