Stony Brook University
The Graduate School

Doctoral Defense Announcement

Abstract

Anti-cancer mitochondrial metabolism drug, CPI-613, induction of catastrophic ATP depletion and cellular starvation

By

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CPI-613 is a mechanistically novel, first-in-class lipoate analog. *In vitro* and *in vivo*, CPI-613 inhibits tumor cell pyruvate dehydrogenase (PDH) and alpha-ketoglutarate (KGDH), both of which are mitochondrial enzymes used in the tricarboxylic acid cycle. Moreover, CPI-613 has significant clinical activity against pancreatic ductal adenocarcinoma and acute myeloid leukemia malignancies in combination with standards of care for these diseases. However, the details of the processes presumptively leading from PDH/KGDH attack to clinical significance remain largely unexplored. In this work, we show that initial CPI-613 attack on tumor mitochondrial metabolism provokes a chain of homeostatic responses, which drive accelerated consumption of both exogenous and endogenous nutrient stores (including carbohydrates and lipids). This drug-induced accelerated starvation is essential for the induction of tumor cell death in culture at doses observed in patients and under in vivo tumor microenvironment-like nutrient-limited conditions. These metabolic responses to CPI-613 reveal some previously unrecognized features of tumor metabolic regulation. Additionally, we find strong synergies between CPI-613 and potentially clinically useful, mechanistically diverse anti-metabolic agents, *in vitro* and *in vivo*, as predicted by the drug-induced accelerated starvation proposed model. More specifically, cell line differences in nutrient stores account for most or all of the differential in sensitivity to CPI-613 *in vitro* and, apparently, *in vivo*. Clinically viable ways to attack these cell line-specific sources of resistance exist, potentially opening approaches to further improvement in the substantial clinical efficacy of CPI-613. Other details of the investigation reveal unexpected mechanisms for the strong synergy of CPI-613 with several traditional standards of care.

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