



Targeting cancer with tumor-specific therapeutic strategies—metabolic reprogramming beyond the Warburg effect

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Although metabolic reprogramming has only recently been characterized as an emerging hallmark of cancer (1), that cancer cells utilize nutrients differently than non-malignant cells is a principle that was observed almost a century ago. In the 1920's, Otto Warburg identified that tumors demonstrated increased glycolytic flux relative to adjacent normal tissues and had an increased reliance on glycolysis relative to oxidative phosphorylation for ATP production (2). He found that even in aerobic conditions, cancer cells preferentially utilized glycolysis despite its inefficiencies. Thus, the concept of targeting a tumor cell's source of nutrition as an anti-cancer strategy became a viable approach. We have selectively targeted colon cancer cells by exploiting their propensity for increased glycolytic flux using a non-metabolizable glucose analog to enhance sensitivity to TRAIL-induced apoptosis (3). In this system, by allosterically inhibiting hexokinase and competitively inhibiting phosphohexose isomerase, colon cancer cells were reprogrammed to upregulate specific death receptors. When combined with TRAIL, these cells experienced increased MEK and ERK activation, leading to colon cancer cell apoptosis via the extrinsic pathway *in vitro* and *in vivo*. Multiple cancers, including colon cancer, utilize increased glucose consumption secondary to oncogenic *RAS* signaling and *TP53* mutations. There has remained a gap in knowledge, however, of how the tissue of origin may affect tumor metabolism, and many *Kras*-driven cancers may have specific metabolic dependencies beyond glucose dependence. Mayers *et al.* have focused on non-small cell lung cancer (NSCLC) and pancreatic ductal carcinoma (PDAC). Interestingly, they have identified that despite

similar genetic mutation initiating events, specific tumor cell's metabolic requirements are met through different sources of nutrition (4).

Even with identical initiating events, NSCLC tumors incorporate branch chain amino acids (BCAA) into proteins and employ these amino acids as a nitrogen source whereas PDAC tumors do not. This correlates well with the response to the levels of BCAA catabolic enzymes (Bcat 1 & 2) in these tissues, where reduced levels of Bcat 1 & 2 slow NSCLC tumor development—which is not observed in PDAC. This data is further supported in mice and humans by plasma levels of BCAA (low in NSCLC and high in PDAC) and tracing studies with ¹³C and ¹⁵N labeled metabolites (α -ketoisocaproate or KIC) derived from BCAA, catabolism to TCA intermediates via *Bckdb*, and levels of BCAA transporters (all high in NSCLC and low in PDAC). All this occurs without change in glycolytic gene expression or *in vitro* cell proliferation following loss of Bcat 1 & 2, which dramatically reduced NSCLC tumor burden following subcutaneous implantation. These findings expand our knowledge regarding specific features of metabolism, in this case BCAAs, in regards to mutation status and cell/tissue type or origin. Such information is likely to have application in other tumor types including glioblastoma (some dependence on *BCAT1*) and those with concomitant cachexia.

This study is truly advancement in the field of research due to its investigation of a specific metabolic feature (branched-chain amino acid metabolism) in two distinct tumor types (lung and pancreatic cancer) with identical oncogene mutation (*Kras*) and tumor suppressor gene (*p53*)

loss. Such a focused effort provides concise information that is confirmed regarding the status of Bcat expression in serum and tissue as confirmed with free and incorporated BCAAs and the enzymes and metabolites involved in their metabolism. The use of elegant *Cre*-responsive models in both lung and pancreas provided the ideal platform for this work. One additional caveat to explore would be deploying an inducible KP system (*Ptf1a-Cre^{ER}*) to target more adult-like pancreas cells. Since *Pdx1* is expressed early in development and is necessary for mouse pancreas development, its ability to drive mutant *Kras* and loss of *p53* occurs very early compared to that of the KP mice induced via viral *Cre* aerosol at 6–12 weeks of age. It is conceivable that in this context, there are small changes in regards to BCAA metabolism in mice, though gene expression in KPC mice employed in these experiments matched human levels of *SLC7A5*, *BCAT*, and *BCKDH*. Another consideration would be metabolic changes in mice with lung and pancreas neoplasia (exclusive mutant *Kras* expression) to determine if features in BCAA catabolism are altered or remain consistent with that in more advanced disease.

Much focus has been placed on metabolomics and cancer, as the prevailing thought is to discover the primary sources of energy for a cancer cell and to work to deprive the unconventional mechanisms that these cells employ to metabolize and use these sources. Yet, most of these studies tend to be rather broad, often not considering distinct indices of these cancers like molecular features, cell type or origin, and specific preferred energy sources; concepts addressed thoroughly in this current study. Extrapolating from this work, it is intriguing to consider that tumors that create a large biomass may require increased amino acid building blocks compared to other tumors. This could have important clinical implications for tumor-specific metabolic inhibition.

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Footnote

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