Editorial

Branched chain amino acid metabolism and cancer: the importance of keeping things in context

Elizabeth M. Selwan, Aimee L. Edinger

Department of Developmental and Cell Biology, University of California Irvine, Irvine, CA 92697-2300, USA

Correspondence to: Aimee L. Edinger. Department of Developmental and Cell Biology, University of California Irvine, Irvine, CA 92697-2300, USA. Email: aedinger@uci.edu.

Comment on: Mayers JR, Torrence ME, Danai LV, *et al*. Tissue of origin dictates branched-chain amino acid metabolism in mutant Kras-driven cancers. Science 2016;353:1161-5.

Submitted Mar 29, 2017. Accepted for publication Apr 18, 2017.
doi: 10.21037/tcr.2017.05.05
View this article at: http://dx.doi.org/10.21037/tcr.2017.05.05

Because non-homeostatic proliferation increases anabolic demand, tumor cells reprogram metabolism in ways that support growth. Although tumor cells retain some metabolic flexibility, the constitutive activation of oncogenes and mutation or loss of tumor suppressors limits their metabolic choices and creates nutrient dependencies not present in their normal counterparts (1-8). Identifying and targeting these differences in metabolic wiring will likely be an effective means to limit tumor growth while sparing normal cells. Clearly, different oncogenic mutations activate distinct downstream gene expression programs that drive metabolic reprogramming in ways that favor certain biosynthetic routes. At the same time, oncogenic events occur in the divergent epigenetic landscapes associated with different tissues of origin. As normal lung and pancreatic cells from the same individual contain identical genomes yet exhibit markedly different gene expression patterns, it stands to reason that tumor cells with shared oncogenic drivers but different tissue origins would do the same. Indeed, a tumor's metabolic signature is more closely aligned with its tissue of origin than with tumors from other tissues (9,10). The tumor microenvironment also provides context that influences metabolic reprogramming by oncogenes. For example, pancreatic ductal adenocarcinomas (PDAC) induce significant stromal desmoplasia resulting in high interstitial pressure and inadequate perfusion (11). Nutrient scavenging strategies such as autophagy and macropinocytosis are likely to be selected for in this cancer class where access to plasma-derived nutrients is limited (12-14). Similarly, spatial metabolic heterogeneity has been noted within individual lung tumors with poorly perfused tumor sections exhibiting distinct metabolic strategies and gene expression profiles compared to better perfused areas (15). In summary, the simplistic view that "cancer metabolism" is defined by aerobic glycolysis (the Warburg effect) and the use of glutamine to replenish TCA cycle intermediates is without a doubt incorrect, failing to capture the complexity, heterogeneity, and context dependence of actual tumor metabolism (8). A recent study by Mayers and colleagues (16) drives this point home, providing robust evidence that the same oncogenic mutations re-program metabolism in distinct ways when they occur in different organs. At the same time, this study also highlights a new metabolic flux in KRAS-driven lung tumors that could be amenable to therapeutic targeting.

Inspired by prior work suggesting that MYC-driven changes in the metabolome differ depending on which tissue hosts the tumor (17), Mayers *et al*. took advantage of the fact that both non-small cell lung cancers (NSCLC) and PDAC commonly exhibit activating mutations in KRAS (e.g., KRASG12D) and loss of the tumor suppressor TP53, both proteins known to modulate metabolic fluxes in cancer cells (2,6,18). Upon Cre expression in either the lung (via adenovirus) or the pancreas (transgenic expression), $Kras^{LSLG12D/+}$; $Trp53^{flox/flox}$ mice develop NSCLC (KP model) or PDAC ($KP^{-/-}C$ model) with similar features

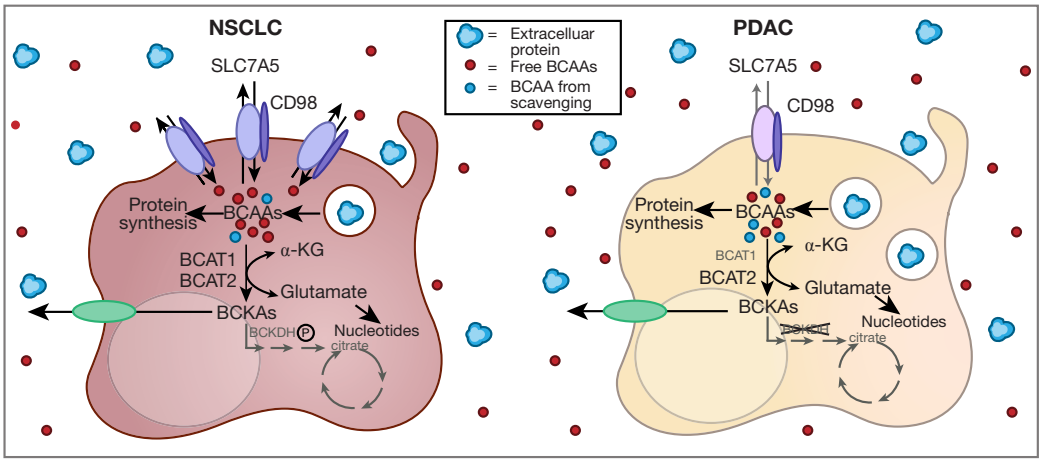

Figure 1 Differential acquisition of BCAAs in KP NSCLC and KP$^{-/-}$C PDAC as described by Mayers *et al.* (16). Relative to normal tissue, SLC7A5 and BCAT1 were over-expressed in NSCLC but not PDAC; BCAT2 protein levels increased in both NSCLC and PDAC. BCKDH was inactivated by phosphorylation in NSCLC while in PDAC BCKDH total protein was greatly reduced. Isotopic labeling studies indicated that carbon from circulating BCAAs ended up in protein and BCKAs in NSCLC to a greater extent than in PDAC. Nitrogen from dietary leucine was used for BCAT-dependent nucleotide synthesis in NSCLC. BSA degradation in the lysosome was increased in isolated PDAC cells relative to NSCLC cells suggesting that PDAC cells may rely on macropinocytosis to compensate for reduced import of extracellular BCAAs through SLC7A5. BCAA, branched chain amino acid; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; BCKDHA, branched chain ketoacid dehydrogenase E1 alpha; BCAT, branched chain amino acid transferase.

to the respective human disease. Using a single genetically engineered mouse model with differential expression of Cre permitted an 'apples to apples' comparison of the metabolic strategies utilized by tumors arising in these distinct anatomical sites. By studying autochthonous tumors *in vivo*, it was further ensured that nutrient and oxygen levels were in the physiologic range; metabolic fluxes in KP NSCLC cells differ significantly *in vitro* and *in vivo* (19). The Vander Heiden group had also previously reported that circulating branched chain amino acids (BCAAs) increase in KP$^{-/-}$C mice with PDAC as a consequence of muscle breakdown while plasma BCAAs decrease in the KP NSCLC model (20). The current study (16) sought to explain this difference, uncovering a reciprocal increase in BCAA levels in lung but not pancreatic tumor tissue. This result suggested that NSCLC and PDAC tumor cells with activated KRAS and loss of TP53 exhibit differential uptake and utilization of BCAAs.

The BCAAs, leucine, isoleucine, and valine, are essential amino acids and must be acquired from the diet. Once they enter cells, BCAAs are either incorporated directly into proteins or metabolized (21) (*Figure 1*). In a reversible reaction catalyzed by the enzyme branched chain amino acid transferase (BCAT), the BCAA amino group is transferred to α-ketoglutarate to produce glutamate and a branched chain α-ketoacid (BCKA). BCKAs can be converted back to BCAAs or oxidized through a series of additional enzymatic steps and eventually enter the TCA cycle if cells express the required complement of enzymes. BCKAs as well as certain other BCAA metabolites can also be secreted and used by other tissues. To understand why mice with NSCLC and PDAC exhibited differences in plasma BCAA levels, Mayers and coworkers tracked the fate of dietary BCAAs in normal tissues and NSCLC or PDAC tumors by feeding mice a diet containing U-^{13}C-labeled leucine and valine. These metabolic tracing studies revealed that, relative to normal lung, NSCLC convert more dietary free BCAA into protein and use BCAT to produce more of the leucine-derived BCKA α-ketoisocaproate (KIC); BCAA carbon entry into the TCA cycle was not altered by KRAS expression or TP53 loss. In contrast, when KP$^{-/-}$C PDAC cells were compared to normal pancreas, less dietary BCAA carbon ended up in proteins and production of KIC from free BCAAs in plasma did not increase significantly. In addition, less labeled free BCAA carbon entered the TCA cycle in PDAC than in normal tissue. Consistent with the observed

changes in labeled KIC in NSCLC, BCAT1 and BCAT2 protein levels were increased relative to normal tissue; BCAT1 protein levels were decreased in PDAC tumors although BCAT2 was up-regulated. U-^{15}N-leucine labeling studies showed that the increase in BCAT1/2 protein in NSCLC correlated with increased use of BCAAs as a nitrogen source for nucleotide synthesis. Aspartate, which in these KP NSCLCs was produced from BCAT-dependent glutamate production, is a critical precursor for nucleotide synthesis in proliferating cells (22,23). Taken together, these results indicate that KRAS activation and TP53 deletion in NSCLC increase the uptake of BCAA from plasma to provide precursors for protein and nucleotide synthesis. PDAC cells, in contrast, did not increase their use of plasma-derived BCAAs for protein synthesis or BCKA production.

It is important to recognize that the failure of PDAC tumor cells to increase utilization of plasma BCAAs does not mean that BCAA transamination is not important in PDAC tumor cells. Indeed, BCAT2 protein levels are significantly increased in KP$^{-/-}$C PDAC in this study, and BCAT2 over-expression can drive the growth of PDAC cells lacking malic enzyme 2 (16,24). It is interesting to speculate that there may be an advantage to using BCAT and BCAAs rather than other amino acids to produce glutamate. Similar to increases in BCAT1/2 and inhibitory phosphorylation of BCKDH in NSCLC, the up-regulation of BCAT2 and the near complete loss of the branched chain ketoacid dehydrogenase E1 alpha (BCKDHA) protein in PDAC tumors would raise BCKA levels suggesting that BKCAs may have an important role in both NSCLC and PDAC. Like tumor cells, activated T cells alter their metabolic program to fuel their rapid expansion during an immune response. Activated T cells take up extracellular leucine at an accelerated rate and increase BCAT1 levels 20-fold to produce glutamate, resulting in the release of the leucine-derived BCKA KIC which accumulates because BCKDH activity is again low (25). That BCAAs are also used to produce glutamate in rapidly proliferating lymphocytes suggests that producing BCKAs may be directly or indirectly beneficial for anabolic cells. Intriguingly, a product of valine oxidation that is secreted from muscle cells, 3-hydroxyisobutyrate (3-HIB), promotes fatty acid transport across endothelial cells leading to an increased lipid supply for muscle cells (26). Proliferating cells require fatty acids to produce membranes for daughter cells (5). Although 3-HIB production requires BCKDH activity which is low in T cells and these cancer cells (16) (*Figure 1*), other BCAA metabolites might have related roles in tissue crosstalk. There are many unknowns and conflicting results regarding the role of BCAAs and their metabolites in controlling feeding behavior and whole body metabolism. Viewing the tumor as an "organ" that may produce and receive signals from other tissues may be important to fully understand the roles of BCAA and their breakdown products in proliferating cells.

The failure of KP$^{-/-}$C PDAC tumor cells to increase their use of plasma BCAA may stem from the down-regulation of both the BCAA transporter protein, SLC7A5, and BCAT1 following transformation by KRAS activation and TP53 deletion (16). Over-expressing SLC7A5 in cell lines derived from KP$^{-/-}$C PDAC tumors increased leucine uptake slightly *in vitro* but did not confer a growth advantage in culture. However, SLC7A5 may increase PDAC tumor growth *in vivo* as subcutaneous tumors formed by one clone of SLC7A5 over-expressing PDAC cells narrowly missed being called as significantly larger than controls (P=0.06). A couple of caveats to this experiment further suggest that low SLC7A5 expression should not be discounted as limiting for PDAC tumor growth. For one, SLC7A5 is an obligate exchanger and must couple influx of BCAAs to the efflux of another substrate (27). Expressing SLC7A5 alone without concomitant up-regulation of another amino acid transporter or BCAT1 over-expression to create a gradient for BCAA import may have limited BCAA uptake. Moreover, SLC7A5 expression in the absence of the heavy chain SLC3A2 that stabilizes SLC7A5 at the plasma membrane may have compromised cell surface expression (28,29). It is not clear that the over-expression strategy employed was sufficient to raise leucine uptake in PDAC cells to biologically significant degree that would match uptake in NSCLC cells. SLC7A5 is over-expressed in many cancers and is a negative prognostic indicator suggesting that this transporter often plays a key role in oncogenesis (30-34). Rather than suggesting SLC7A5 is not important in PDAC, the work of Mayers *et al*. implies that low SLC7A5 expression levels in PDAC may result in enhanced sensitivity to inhibitors. JPH203, a small molecule SLC7A5 inhibitor effective as a single agent in some tumors (35) has advanced to a clinical trial (UMIN000016546) and thus the sensitivity of both PDAC and NSCLC to this agent is worth evaluating.

Although SLC7A5 levels were low in KP$^{-/-}$C pancreatic tumors, RAS-driven cancers have an alternate means of obtaining amino acids: catabolism of extracellular protein via macropinocytosis (12,13,36). Intriguingly, while bovine

serum albumin was taken up and degraded in lysosomes in both tumor types, Mayers *et al*. observed that $KP^{-/-}C$ PDAC cells catabolize albumin to a greater extent than KP NSCLC in cell culture leading them to hypothesize that the relative amount of macropinocytosis in these tumor classes may relate to their differential ability to acquire leucine from the environment (*Figure 1*). As alluded to above, this hypothesis would make sense given the significant differences in perfusion in these two tumor classes. However, given that albumin is consumed through macropinocytosis-dependent and -independent pathways (37) and that nutrient-sensitive signal transduction pathways regulate macropinocytosis, quantifying the relative dependence of NSCLC and PDAC on amino acids obtained through macropinocytosis will require additional experiments. The effect of adaptation to cell culture on the relative levels of macropinocytosis must also be considered. In our hands, A549 human lung cancer cells with activating mutations in KRAS exhibit as robust macropinocytosis of high molecular weight dextran as pancreatic cancer cell lines with KRAS mutations (unpublished data). *In vivo* studies in NSCLC to match those recently performed by this group in autochthonous PDAC tumors (38) will certainly be informative.

Perhaps the most striking result in this report was obtained when the authors directly tested their conclusion from stable isotope labeling studies: BCAT activity is essential for the growth of KP NSCLC but not $KP^{-/-}C$ PDAC tumors. They created genetically matched *Bcat1/2* null NSCLC and PDAC tumor-derived cell lines differing only in their epigenomes using CRISPR/Cas9 mediated gene editing. Both NSCLC and PDAC cells proliferated normally *in vitro* despite *Bcat1/2* deletion. Strikingly, loss of *Bcat1/2* crippled NSCLC tumors grown either subcutaneously or orthotopically in the lungs of syngeneic hosts. In contrast, the subcutaneous growth of PDAC tumors was unaffected by *Bcat1/2* deletion. Some growth inhibition was apparent when *Bcat1/2* PDAC tumors were grown orthotopically suggesting that BCAT2 up-regulation may be important in these tumor cells in the context of the pancreatic microenvironment. It is worth noting that BCAT2 activity is required even in standard culture medium in the subset of PDAC where malic enzyme 2 is deleted (24), an event not modeled in $KP^{-/-}C$ mice. An important conclusion from the divergent *in vitro* and *in vivo* results with BCAT-deficient KP NSCLC cells in Mayers *et al*. is that *in vitro* screens designed to elucidate metabolic liabilities in tumor cells may produce misleading results. Cell culture media formulations were developed to maximize cell proliferation, and reducing nutrients to more physiologic levels often uncovers metabolic dependencies that are not apparent when nutrients are present in large excess. A case in point is the similar disconnect in the *in vitro* and *in vivo* dependence of tumor cells on glutaminase (GLS), the enzyme that converts glutamine to glutamate. GLS was essential in KP NSCLC cells *in vitro*, but GLS inhibitors failed to limit tumor growth *in vivo* (19). It would be informative to test whether culturing KP NSCLC cells in more physiologic levels of nutrients would elicit a proliferation or survival defect upon *Bcat1/2* deletion. If so, conducting metabolic screens in more physiologic nutrient levels might dramatically increase their translational value. Alternatively, other differences between the tumor microenvironment and the cell culture dish that could prove more difficult to identify and mimic *in vitro* might be responsible for the divergence between cell culture and *in vivo* results. Either way, these studies with *Bcat1/2* deleted cells (16) provide a cautionary tale and emphasize the importance of characterizing metabolic pathways *in vivo*.

The work of Mayers *et al*. also suggests new therapeutic approaches for NSCLC. With the caveat that a chemical inhibitor and/or conditional alleles of *Bcat1/2* will be required to formally confirm that inhibiting BCAT in an established tumor will stop growth or cause tumor regression, BCAT inhibitors could have value in NSCLC. An important first task will be to determine whether both BCAT1 and BCAT2 should be inhibited or whether targeting only one of these paralogs will be sufficient to slow tumor growth while minimizing toxicity. *Bcat1* is expressed primarily in the brain of mature healthy mice, but BCAT1 is dramatically induced in activated T cells and BCAT1 is over-expressed in several cancers consistent with *Bcat1*'s designation as a MYC target gene (25,39-42) (*Table 1*). IDH^{WT}, but not IDH^{mut}, glioblastomas also require BCAT1 for growth both *in vitro* in standard medium and *in vivo* (48). Interestingly, while the levels of the mitochondrial isoform, BCAT2, are not altered by T cell activation (25), *Bcat2* is an SREBP1 target gene whose expression is negatively regulated by AMPK, and in certain genetic contexts BCAT2 over-expression can drive PDAC growth while knocking down Bcat2 limits colony formation (24). BCAT2 protein levels did increase in $KP^{-/-}C$ PDAC tumors (16) relative to normal tissue, and the Human Protein Atlas suggests that BCAT2 is expressed at high levels in other human cancers as well. Taken together, these findings suggest that both isoforms of BCAT may contribute to tumor growth, but inhibiting BCAT1 will likely be necessary and might be

Table 1 Comparison of the two BCAT isoenzymes

Variables	BCAT1	BCAT2
Other names	BCATc (cytosolic)	BCATm (mitochondrial)
Tissue distribution	Brain, gonads, activated CD4+ T-cells (25)	Most tissues, excluding liver (43,44); high in exocrine pancreas (44)
Knockout phenotypes	Activated *Bcat1*$^{-/-}$ murine T-cells exhibit elevated mTORC1 signaling and glycolytic metabolism (25); *bcat-1* null *C. elegans* have an extended lifespan and healthspan (45)	*Bcat2*$^{-/-}$ mice have high circulating BCAAs, improved insulin sensitivity and glucose tolerance, and elevated energy expenditure (46); *Bcat2*$^{-/-}$ mice have lower exercise capacity (47); required in subset of PDAC (24)
Expression in cancer cells	Over-expressed in: glioblastoma (48); nasopharyngeal carcinoma (39); cancers with elevated MYC? (39)	Over-expressed in: PDAC (KP$^{-/-}$C model) (16); cancers with active SREBP1 and low AMPK activity? (24)

BCAT, branched chain amino acid transferase; PDAC, pancreatic ductal adenocarcinoma.

sufficient to cause tumor growth inhibition in NSCLC. Encouragingly, *Bcat1* whole-body knockout mice exhibit no overt defects suggesting that BCAT2 can compensate for the loss of BCAT1 (*Table 1*) (25). In fact, impairing *bcat-1* expression in *C. elegans* extended maximum lifespan by 25% and mean lifespan by 19%, further supporting that BCAT1 inhibitors may not be toxic (45). In this study in worms, however, the beneficial effects of BCAT-1 loss depended on mTORC1 activation downstream of leucine accumulation. *Bcat1*$^{-/-}$ T cells also exhibit higher BCAA levels, mTORC1 activation, and increased glycolysis (25). Given that mTORC1 activation and glycolysis are associated with anabolism in many cancer cells, it will be important to empirically test whether small molecule BCAT1 inhibitors would have undesirable effects on tumors or whole body metabolism. It is also important to recognize that more than one node in a pathway and/or compensatory pathways must often be targeted simultaneously for metabolic inhibitors to exhibit sustained effects and to tip the balance from a cytostatic to cytotoxic effect that might lead to tumor regression. Given the dramatic up-regulation of SLC7A5 observed here in NSCLC (16), small molecule inhibitors of SLC7A5 (35) and/or macropinocytosis inhibitors (13) could be logical choices for combination with inhibitors of BCAT1.

In summary, this study by Mayers *et al*. establishes that tissue of origin profoundly influences BCAA flux in response to KRAS activation and loss of TP53, suggests a new therapeutic strategy in NSCLC, and demonstrates that *in vitro* screening of metabolic inhibitors under standard tissue culture conditions is likely a flawed strategy. At the same time, many important questions are raised that will need to be addressed by future studies. Clearly, the successful therapeutic application of metabolic inhibitors in the clinic will require a more complete understanding of the roles of the tumor and tissue microenvironment, oncogenic mutations, and epigenetic landscape in shaping the metabolic choices and dependencies of different tumor classes.

Acknowledgments

Funding: EM Selwan was supported by T32-CA009054-37. AL Edinger was supported by grants from the NIH (R01 GM089919), CDMRP (W81XWH-15-1-0010), and the UC Cancer Research Coordinating Committee (CRR-17-426826).

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Zhen-Yu Lin (Cancer Center, Union Hospital, Huazhong University of Science and Technology, Wuhan, China).

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2017.05.05). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Selwan EM, Edinger AL. Branched chain amino acid metabolism and cancer: the importance of keeping things in context. Transl Cancer Res 2017;6(Suppl 3):S578-S584. doi: 10.21037/tcr.2017.05.05

