Metabolic markers as cancer clues

Changes in branched-chain amino acids may be first sign of certain cancers

By Jared R. Mayers

The study of cancer metabolism began almost a century ago when Otto Warburg noted that cancerous tissues metabolize glucose differently from their normal counterparts (1). It has since become widely understood that cancer cells, and proliferating cells more broadly, carry out a metabolic program that favors the accumulation of new biomass components by synthesizing amino acids, lipids, and nucleotides necessary for the generation of daughter cells (2).

Contemporary studies have focused on cell-autonomous metabolic alterations in cancer, using cell culture models to dissect the contributions of different oncogenes and tumor suppressors to observed metabolic phenotypes (3). These systems have yielded numerous promising therapeutic targets (4), although their nonphysiologic nature raises the question of how broadly findings may apply to patients (3). In fact, models deviating from standard culture conditions have uncovered previously underappreciated metabolic flexibility within cancer cells (2), and growing the same cell line either in culture or in animals alters the fuel these cells use (5).

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Based on these findings, we posited that evaluating metabolism in mouse models of cancer and in human subjects might better identify metabolic weaknesses in cancer cells that could be exploited therapeutically. Specifically, we sought to determine how cancer can influence whole-body metabolism through interactions with normal cells and the tissue microenvironment, particularly in early-stage disease.

Initially, we focused on pancreatic cancer, a leading and increasingly common cause of cancer death in the United States (6). Pancreatic cancer is disproportionately associated with systemic metabolic alterations such as insulin resistance (7) and cachexia, a condition characterized by wasting of muscle and fat, which is commonly seen in end-stage disease (8). Although these phenotypes are well documented, it was unknown whether more subtle metabolic changes, such as alterations in circulating nutrient levels, could yield insight into earlier time points of disease development.

A METABOLIC INDICATOR OF EARLY PANCREATIC CANCER EMERGES

We used mass-spectrometry metabolomics to analyze samples from four prospective human cohorts and found an association between elevated plasma levels of branched-chain amino acids (BCAAs) and future diagnosis of pancreatic cancer (9). Intriguingly, this association was strongest 2 to 5 years before diagnosis, a period hypothesized to overlap with occult disease (10). Thus, although these cohort studies are traditionally used to identify risk factors for future disease development, our findings indicated that BCAA elevations might instead represent a marker of early pancreatic cancer.

We recapitulated these observations in two mouse models of pancreatic cancer driven by mutations in Kras and Trp53 and confirmed our hypothesis from the human data that the changes occurred during the earliest histologic stages of invasive disease. Using stable isotope–based labeling, we demonstrated that elevated plasma BCAAs resulted from increased systemic protein turnover, most likely due to protein degradation in the muscle. This suggested that the process of tissue breakdown that is associated with cachexia during end-stage disease likely begins years earlier in humans than previously thought (9).

In this study, we used a reverse-translational approach, taking human data into mouse models, which allowed us to dramatically shift how we study prospective human cohorts and to exploit the variable lengths of time from blood draw to cancer diagnosis to study early disease. As a result, we were able to understand a mechanism of early disease progression and not just predictors of disease development and diagnosis.

CIRCULATING INDICATORS OF ALTERED METABOLISM ARE ALSO PRESENT IN LUNG CANCER

After demonstrating that one type of cancer could drive whole-body metabolic alterations, we wondered whether these effects might occur across other cancer types. To allow for a direct comparison, we chose to investigate plasma metabolite alterations in another Kras- and Trp53-driven model of cancer: non-small-cell lung carcinoma (NSCLC).

In contrast to our observations in the isogenic pancreatic cancer model, plasma levels of BCAAs were decreased in NSCLC tumor-bearing mice (11). Using stable-isotope BCAA tracers, we observed that NSCLC cells, but not pancreatic cancer cells, take up more free BCAAs compared with their respective tissues of origin.

NSCLC cells incorporate plasma BCAAs into proteins and additionally use them as a source of nitrogen for de novo synthesis of nonessential amino acids and nucleotides (11). This activity drives the decreased plasma BCAA levels observed in this model (see the figure). Pancreatic cancer cells, on the other hand, rely more on the uptake and metabolism of material from the surrounding stromal environment to obtain...
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Early pancreatic cancer and non–small-cell lung carcinoma (NSCLC) are associated with distinct changes in plasma branched-chain amino acids (BCAAs). In contrast, NSCLC cells take up more free BCAAs, resulting in decreased concentrations.

In pancreatic cancer, increased protein turnover and muscle breakdown with concurrent low utilization by tumor cells drive increased levels of BCAAs.

Branched-chain amino acids and cancer

Importantly, factors that influence metabolism, in addition to genetics, are important factors that influence metabolic weaknesses for a given tumor. Consistent with this idea, administration of chemotherapies that target nucleotide metabolism has historically been based on tumor type rather than genetics (18).

Using mouse and human data, we have explored metabolic interactions between nascent tumors and their host environment, both local and distant, which measurably influence whole-body metabolism. Exploring the mechanisms driving these changes has altered our interpretation of prospective human cohort data, opening new avenues of investigation into early disease. Additionally, our work on the combined influence of mutational status and tissue context on a tumor’s metabolic preferences resulted in our identification of a previously unappreciated, cancer-type-specific metabolic vulnerability that could be targeted therapeutically.

Our work expands the promise of precision-medicine approaches to targeting cancer metabolism. Continued investigation with in vivo systems remains our best hope, both to understand the metabolic features of early cancer development and to develop strategies to exploit these features therapeutically.

REFERENCES AND NOTES

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