



Contents lists available at ScienceDirect

EBioMedicine

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Commentary

Metabolomics reveals intratumor heterogeneity – Implications for precision medicine

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ARTICLE INFO

Article history:

Received 21 April 2017

Accepted 21 April 2017

Available online xxx

Cancer cells have altered metabolism and ongoing efforts in developing therapies that target cancer metabolism are showing promise (DeBerardinis and Chandel 2016). However, these therapies show variable efficacy and whether the source of this variation is linked to the metabolic differences across or possibly within individual tumors is unknown. In this issue of EBioMedicine, Okegawa et al. use metabolomics to not only demonstrate differences across human kidney tumors, but they also identify metabolic differences within regions of the same tumor (Okegawa et al. 2017). The incorporation of these results into the strategy of investigational therapies may lead to more precise patient stratifications according to their metabolism.

The intertumor heterogeneity of gene expression has been widely appreciated (Hu et al. 2013). For example, gene expression signatures are now routinely used clinically to guide treatment decisions as is the case of whether to use chemotherapy after surgical resection in early stage breast cancer (Cardoso et al. 2016). In contrast to what has been achieved with gene expression, predictive models based on metabolism have not been widely used. This is because many challenges remain for using metabolomics approaches clinically in cancer. In addition to the genetic makeup of the tumor cells, tumor metabolism can be largely affected by environmental factors (Vander Heiden and DeBerardinis 2017), such as the location of the tumor origin, positioning of the vasculature, nutrient availability in the plasma that can be affected by diet, liver function and gut microbial composition, and interactions with stromal cells such as the immune compartment and endothelial cells. Thus, the complexity of the sources of variation within and across tumor tissues has limited translational applicability.

With current technology, metabolomics data can be acquired from human samples. For instance, from performing metabolite profiling on 138 matched human kidney tumors and normal tissue pairs, a recent study was able to group kidney cancers according to their metabolic

profiles and associate particular sub-groups with poor-survival (Hakimi et al. 2016). Furthermore, noninvasive approaches using isotope tracing have been employed to measure the flow of nutrients through metabolic pathways in patients. For example, Fan et al. performed a ^{13}C glucose infusion in human lung cancer patients prior to surgery (Fan et al. 2009). They identified increased pyruvate carboxylase (PC) activity in human lung tumors as compared to the surrounding normal lung. Hensley et al. further demonstrated that human tumors exhibit not only altered tumor metabolism compared to what is observed in adjacent benign lung, but also significant intertumor and intratumor heterogeneity in tumor metabolism by employing clinical imaging and intraoperative ^{13}C -glucose infusions in human lung tumors (Hensley et al. 2016). Other metabolomics studies in ovarian cancer have demonstrated that signatures of drug response may be contained in the metabolite profiles of human tumors obtained from surgical resection (Liu et al. 2016).

Now Okegawa et al. not only characterized distinct metabolic profiles across human kidney tumors but also in different regions of the same tumor. By measuring metabolites in spatially-separated sites within human kidney tumors and performing unsupervised clustering, they first identified two clusters (MC1 and MC2) with MC2 exhibiting features associated with increased pyruvate metabolism. They further confirmed their results via stable isotope tracing in tumor slices. Interestingly, these differences were not associated with genetic variation, which further indicates that multiple factors contribute to the heterogeneity of cancer metabolism. While metabolomics can show that there are changes in pathway activity, the data don't directly imply that the pathways identified are required. Therefore, Okegawa et al. treated patient kidney tumor derived cell lines and xenografts with the mitochondrial pyruvate carrier inhibitor, UK5099, to demonstrate that targeting pyruvate metabolism could be therapeutic in some kidney cancers. Beyond identifying this therapeutic target, Okegawa et al. further showed that distinct metabolic patterns could be linked to the efficacy of the clinically used kidney cancer drug, temsirolimus.

Characterizing cancer metabolism and evaluating its predictive capability in patients faces many challenges. Both patient genetic lesions and environmental factors contribute to reprogrammed cancer metabolism and it is hard to identify exhaustively each of these factors in a patient cohort which limits any population analysis. Also, conclusions can grossly vary depending on the experimental model used to collect the metabolic signature and validate its function, which makes it difficult to extrapolate findings from experimental models to human situations. Nevertheless, future work will evaluate pyruvate transport into the

DOI of original article: <http://dx.doi.org/10.1016/j.ebiom.2017.04.009>.

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mitochondria as a therapeutic target and predictor of temsirolimus sensitivity in broader contexts. The work from Okegawa et al. however makes a major step forward in revealing the heterogeneity of metabolism in human kidney cancer and demonstrates that metabolic phenotypes are complex yet tractable with the appropriate technology, and once identified, could potentially have substantial clinical value for precision medicine.

Disclosures

The authors declare no conflicts of interest at this time.

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