In an era of ctDNA, is metabolomics the new kid on the block?

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05/07/2015; US Patent No: 20190136238, 05/09/2019; International Patent No: WO2013177426-A2, 04/23/2015).

Summary

Mass action drives the serum homeostasis of metabolites. Recent developments in biofluid metabolomics suggest the potential to harness these changes using small volumes of blood to diagnosis, monitor, and risk stratify cancer patients. This current study may represent a complementary technology to circulating tumor DNA detection.

Main body

In this issue of *Clinical Cancer Research*, Larkin and colleagues (1) harness metabolomics to prospectively identify cancer in the “low-risk, but not, no risk” patient group. This is the group of patients for which the probability of cancer is low on the clinical differential diagnosis, but where a delay in diagnosis may occur due to non-specific symptoms. In managed healthcare, such as the UK National Health Service, cancer referral pathways have a two week wait period for non-specific symptoms such a fatigue or weight loss. To address this, Suspected CANcer (SCAN) pathway was established in Oxfordshire, UK to help identify patients with early stage cancers. Patients were evaluated with contrast enhanced computerized tomography (CT) scans of the chest, abdomen, and pelvis alongside blood tests to help establish a diagnosis. This allowed for a gold standard to be used to call malignancy versus non-malignancy. Nuclear Magnetic Resonance (NMR)-based biofluid metabolomic analysis was then used to determine if could aide in the detection of cancer. The authors found that metabolomics demonstrated a relatively sensitive and specific test that could be used as a cost effective screen prior to ordering CT scans. While in the United States efforts are being made to use modalities such as circulating tumor DNA (ctDNA) or low dose CT scans to identify early stage cancers, these are not as of yet highly cost effective for population based screening.

The analysis of ctDNA is a rapidly advancing field used for disease monitoring, early detection, and genomic biomarker analysis hastened by the need for an accurate, rapid, and predictive test that can inform treatment decisions. Indeed, the use of ctDNA is making its way into clinical practice and being validated by clinical trials. For example, ctDNA based molecular residual disease (MRD) has been used in non-small cell lung cancer perioperatively, where it was able to risk stratify MRD positive and MRD-negative patients for the potential of relapse (2). In addition, pretreatment ctDNA was able to predict response of melanoma to first-line immunotherapy (3).

The promise of ctDNA is not without is technical challenges. While ctDNA allows for the real-time genomic profiling without tumor biopsies, it is hindered by the low proportion of of ctDNA (%) in circulation and the sequencing requirements needed for accurate detection. Whole genome sequencing or even whole exon sequencing at a depth needed for detection is still prohibitively expensive for routine monitoring. In addition, the blood volumes required for detection are not trivial, for example the Natera test requires 10 milliliters of blood per draw. Depending on the technology used, amplification with PCR may be needed prior to sequencing and this can lead to background errors which may masquerade as tumor-derived variants. As these technologies improve, there is the expectation that ctDNA detection and utilization will improve and become more cost effective (4). In the meantime, there is a window of opportunity for alternative approaches to detect and monitor cancer.

One such opportunity comes from the paradigm shifting work of Rabinowitz group at Princeton University published in Nature Metabolism on circulating metabolite homeostasis (5). Using small animal *in vivo* carbon tracing of amino acids, glucose and other metabolites, they found a linear relationship between consumption flux and circulating concentration of metabolites. This observation suggests that mass action kinetics drive the concentration of circulating metabolites. Extrapolation of this concept to cancers, posits that blood steam metabolites would be proportional to the mass produced and released into the blood stream by a tumor. Complications implementing these concepts undoubtedly exist, including the fasting/fed state and resultant endocrine biology. Nevertheless, the work illustrates that an opportunity may exist to use steady state of metabolites in the blood stream as a first screen for cancer.

This leads us to the current work by Larkin et al. (1) This current research describes a new minimally invasive and inexpensive blood test to identify cancer in patients with non-specific symptoms in order to determine if the cancer has spread. The study analysed samples from 304 patients with non-specific symptoms of cancer, such as fatigue and weight loss, who

were recruited through the Oxfordshire Suspected CANcer (SCAN) pathway. Unlike many blood-based tests for cancer, which use genetic material from tumours, this test measures the levels of small molecule metabolites NMR metabolomics. This rapid and inexpensive test has the possibility of identifying malignancy before conventional imaging, which could lead earlier cancer diagnosis, more appropriate treatment, and hopefully improve outcomes. Therefore, it is very exciting that the technology is showing promise in detecting cancer.

If metabolomics can be developed as a small blood volume test that can be rapidly turned over as a screen, this will be of high value to the primary care physician. However, in order to implement this methodology, it will be necessary to know the number of patients needed to find a true positive, as well as the positive and negative predictive values of the test. The likelihood a patient will be missed by any one test is critical to making public health decisions. As the price for sequencing comes down, we may find complementary information in utilizing both metabolomics and ctDNA testing. While one may have a higher sensitivity and require less volume, the ctDNA test can yield actionable information about point mutations and genetic predisposition. The clinical strengths of each test are demonstrated in **Figure 1**.

As both tests are used mainly as screens, only a biopsy and formal pathologic diagnosis at this time can truly make a diagnosis of cancer. Therefore, while biopsies and CT scans will not be leaving the current practice of oncology in the foreseeable future, ctDNA and metabolomics may soon become paired companion diagnostic approaches. These tests have the potential to detect early treatment failures and prevent unneeded toxicities from ineffective therapies long before a CT scan can formally identify a difference. As such, let us welcome the development of metabolomics to the management of cancer as a potential new player on the block.

Figure Legend

Figure 1: Metabolomics (left) and ctDNA (right) are potentially complimentary technologies aimed at improving the care of cancer patients.

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