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Metabolic profiling: are we en route to better diagnostic tests for cancer?

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Cancer is a major health problem worldwide; in the USA alone over 1.5 million cancer incidences are reported each year and cancer accounts for one in four deaths [1]. Currently, cancer diagnosis involves the use of one or more radiological modalities such as x-ray, computed tomography, MRI or ultrasound, as well as confirmatory tests involving histopathological examination of biopsied tissue from the suspected region. Radiological methods are generally useful for detecting and locating advanced-stage cancer. However, they are much less effective for detecting lesions in the early stages of cancer or cancers that show little or no imaging abnormalities. The inaccessibility of some organs, the pancreas for example, due to their deep anatomical location, makes their cancer diagnosis by radiological means ineffective. Because of these and related reasons, the performance of contemporary methods for detection of early-stage cancers continues to be insufficient. For example, mammography misses 20–40% of small breast tumors, especially in younger women.

Earlier cancer detection offers numerous opportunities for effective treatments; it improves survival rates for cancer patients and reduces social and financial burden. Therefore, interest in the development of effective and reliable methods for early cancer diagnosis has long been an important goal [2]. In addition, better diagnostic methods for detecting cancer recurrence, for predicting therapy and for stratifying patient risk are also highly desired. A sizable number of blood- or tissue-based molecular markers including α-fetoprotein, cancer antigens, carcinoembryonic antigens, prostate-specific antigens, circulating tumor cells and, recently, genetic markers have been developed for cancer diagnosis, therapy monitoring or prediction, and recurrence surveillance. In most cases, however, these markers are not

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sufficiently sensitive or specific to detect cancer at an early stage, or its recurrence at an early time point.

Beyond proteins, genes or other cellular markers, metabolites provide an alternative and promising approach to detect cancer. Metabolic profiling has emerged as a powerful methodology for understanding biochemical systems and their responses to a variety of stimuli including disease processes. A variety of promising applications have been explored in numerous areas such as early disease detection (including several cancers), detailed studies of biochemical mechanisms and pathways, pharmaceutical development, toxicology and nutritional studies, among others [3–6]. The field of metabolomics focuses on the parallel measurement of hundreds of small molecule metabolites in biological samples such as blood, urine and biopsied tissue, which are obtainable by noninvasive or minimally invasive methods. Since metabolite levels are sensitive to subtle differences and changes in the pathological status, metabolic profiling promises novel avenues for early disease detection as well as a better understanding of disease processes.

Historically, cancer metabolism is known to be altered to allow the disease to grow rapidly and proliferate [7]; the well-known Warburg effect now provides the basis for cancer PET imaging. More recently, new studies indicate that cancer metabolism is ever more complicated as shown, for example, by the discovery of a glutamine addiction in glyoma cells [8]. These and other related findings provide a number of avenues for developing new cancer diagnostics as well as information on potential drug targets through the identification of associated enzymes and transcription factors that are also altered in cancer.

Metabolic profiling is performed using an array of powerful analytical techniques that include mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy along with multivariate statistical methods. The two analytical techniques, NMR and MS, are complementary in nature. While NMR is highly reproducible and quantitative, MS is highly sensitive and enables access to hundreds or even thousands of metabolites in a single measurement. Advanced multivariate statistical methods [9] and available software packages provide powerful but accessible tools for data reduction, analysis and predictive model building. As a result of recent advances in instrumentation, experimental methodologies, databases and data analysis approaches, a number of bottlenecks associated with reliable metabolite analysis have been overcome [10–14].

A popular approach in metabolomics is unbiased global profiling, in which complex NMR or MS data are directly subjected to multivariate statistical analysis for identifying distinguishing metabolite biomarkers. A more robust approach, which is increasingly used, is quantitative metabolic profiling; it involves targeting metabolites associated with pathways that are closely related to cancer or other biological states of interest, and measuring absolute concentrations that can be directly related to other studies. Another promising approach that offers specific information on metabolites under altered genetics or pathological conditions is metabolite flux analysis using stable isotope-labeled substrates. A metabolite and its altered concentration can often be associated with a number of different pathways; however, stable isotope-resolved methods are extremely powerful in unraveling

the contributions from specific pathways and providing unique information on pathways under normal as well as pathological conditions.

Currently, the field of metabolomics is producing a new and sizeable body of knowledge on altered metabolite levels and pathways in cancer. Most studies have focused on distinguishing a variety of cancer patients from matched controls based on measurements of biofluids and excised or biopsied tumors; many of these studies show quite high classification accuracies based on the developed statistical models. An increasing number of studies report the utility of metabolomics for detecting a variety of cancers, and have identified potential metabolite biomarkers. For example, elevated choline metabolites in breast tissue have been shown to have diagnostic value for breast cancer [15]; estrogen receptor, progesterone receptor and lymph node status in breast cancer have been predicted successfully based on metabolite profiling of biopsied tissue [16]. A combined NMR and MS analysis of blood was used to develop a test for the early detection of breast cancer recurrence [17]. In addition, NMR studies showed that low citrate levels in prostatic secretions can be used to diagnose prostate cancer, outperforming prostate-specific antigen [18,19], and tissue-based metabolomics studies have shown that sarcosine is a marker of aggressiveness of prostate tumors [20].

Nevertheless, despite significant advancements in metabolomics methods, the identification of metabolite biomarkers that can distinguish cancer patients from healthy controls and many novel findings on altered cancer metabolism, many challenges persist in developing the routine clinical utility of metabolomics for cancer diagnosis. In general, it has been very challenging to translate molecular biomarkers to clinical practice, whether those markers are genes, proteins or other species. Barriers to progress certainly include externalities such as regulatory issues and limited research funding; however, many biomarker candidates simply do not validate or have sufficiently good performance to become adopted. In addition, a major challenge for metabolomics is the interference by contributions from confounding factors such as diet, age, gender, ethnicity, drugs, lifestyle and environment. The sensitivity of metabolism to biological changes means that metabolite levels are affected not only by disease processes but also by many others. These additional factors need to be better understood and controlled. Contributions from other diseases unconnected to cancer and heterogeneity of tumors, which can significantly affect reproducibility, are also challenges to overcome. With approximately 5000–8000 small molecule metabolites present in the human body (excluding lipids), the identities of most of these are still unknown or at least difficult to measure. Biological specimens used for study are extremely complex; no single analytical technique is currently capable of detecting all the metabolites in a single step and analysis of metabolites with sufficient interlaboratory reproducibility still poses some degree of challenge, specifically for routine MS-based metabolic profiling. These challenges are in fact well recognized and there are already major efforts to overcome them. With close collaborations with clinicians, well-designed protocols are increasingly being developed and followed to eliminate many confounding factors. Investigations using controlled animal models and cancer cell lines help validate findings in human subjects and also help offset confounding factors from tumor heterogeneities to allow a better understanding of limits of metabolite biomarker performance. On the analytical side, there have been constant efforts

to improve sample handling, processing and experimental conditions, and enhance spectral resolution and sensitivity using isotope-labeled methods.

In summary, with its ability to analyze hundreds or even thousands of metabolites with high throughput, metabolomics promises a multitude of applications in cancer diagnostics, ranging from early detection, monitoring treatment and recurrence and therapy prediction, to (more generally) personalized treatment. The efforts underway are already effectively linking the metabolome with genotype and phenotype and providing a better understanding of enzymes and gene function, which promises routes to novel therapeutic treatments and drug development. Improvements in quantitative metabolomics geared towards achieving consistency in results across different analytical platforms and laboratories will lead to standardized analytical protocols, enable direct comparison of findings from different laboratories and validation of results, and contribute to the identification of reliable cancer markers. We anticipate significant progress in cancer diagnostics from the field of metabolomics.

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Biographies

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