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Application of Metabolomics in Cancer Research: As a Powerful Tool to Screen Biomarker for Diagnosis, Monitoring and Prognosis of Cancer

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Abstract

Cancer cells exhibit profound alterations in their metabolism. The process of increased aerobic glycolysis supports cell proliferation and promotes cancer progression *via* alteration of glucose, glutamine and lipid metabolism. In recent years, extensive efforts have been devoted to revealing the mechanisms underlying for metabolic alterations in cancer, thus products of intermediary metabolism has been a topic of considerable research interest over the past decades. Metabolomics is defined as the quantitative measurement of the dynamic multiparametric metabolites. Identification and quantification of intermediary metabolism by metabolomics can better understand the metabolic changes in tumors. Hence metabolic profiling may be of broad utility for investigating the metabolic pathways and molecular mechanism of carcinogenesis, and as the powerful tool to screen the potential biomarkers for the early diagnosis of human cancer and drug responsiveness. This review article will summarize the overview of metabolomics and the target identification in metabolic pathway by metabolomics, as well as the application in cancer diagnosis and prognosis. In addition, we also critically evaluating the limitation of this approach, and present the potential applications of metabolite profiling in development of novel therapeutic strategy for cancer and precision medicine.

Key words: Metabolomics; Biomarkers; Metabolite profiling; Cancer metabolism; Diagnosis; Prognosis; Precision medicine

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Introduction

It has been proposed that metabolic reprogramming is a central feature of cancer, resulting in enhanced glycolysis, and it is also thought to be essential for rapid cancer cell proliferation [1]. Characteristic metabolic changes enable cells to generate more energy and macromolecules for cancer cell growth, proliferation and division. So, targeting cancer metabolism has emerged as a hot area research and a promising therapeutic target for cancer prevention and treatment in recent years.

Biochemical and molecular studies suggest several possible mechanisms of metabolic alteration evolve during cancer development, including mitochondrial malfunction or defects, adaption to hypoxic tumor microenvironment, oncogenic signaling and abnormal metabolic enzymes [2]. The different energy metabolism between cancer cells and normal cells provides therapeutic strategies to preferentially kill cancer cells with metabolism targeted compounds. Alterations of glucose, glutamine and lipid in the process of energy metabolism contribute to cancer cell proliferation and promote cancer progression, which also has become one of the hotspot in cancer research [3-6]. Extensive efforts in recent years have been focused on metabolic alterations in cancer, the products of intermediary metabolism has been a topic of considerable research interest.

As the newest "omics" science, such as genomics, transcriptomics, proteomics or metabolomics, metabolomics is the systematic study of small-molecule metabolites (an atomic mass <1.5 kDa) in living systems [7,8]. Metabolomics is a technology for detection, identification and quantification of intermediary metabolism, and hence may better reflect the biological changes in tumorigenesis [9,10]. Since cancers are known to possess highly unique metabolic phenotypes due to the altered metabolism, metabolic profiling has been proposed as a means of measuring the total complement of individual metabolites in a given biological sample

[11]. Hence metabolic profiling may offer the opportunity to understand the molecular mechanism of carcinogenesis, and as the potential biomarkers for the early diagnosis of human cancer and prognosis in cancer therapy, and even treating cancers.

This review article will summarize the recent development of metabolomics, the application of metabolite profiling in several important aspects of the cancer, including target identification in metabolic pathway, and screen the potential biomarkers for the early diagnosis of human cancer, as well as the monitoring and prognosis in cancer therapy. In addition, we also critically evaluate the limitation of this approach, and present the potential applications in development of novel therapeutic strategy for cancer.

The Overview of Metabolomics

Metabolomics is the scientific study of chemical processes involving metabolites and, specifically, it is the systematic study of the unique chemical fingerprints, mainly on the small-molecule metabolite profiles [12]. The metabolome means collect all metabolites in biological samples, including cell, tissue, organ or organism, which are the end products of cellular processes [13]. So, it not only offers holistic information dynamically responsive to both endogenous and exogenous of living systems to factors, but also detects and identifies global small-molecule metabolic profiles of complex biological matrices. Compared with other omics, such as mRNA gene expression data and proteomic analysis, it will just reveal the data that represents one aspect of cellular function. However, the instantaneous snapshot of the physiology of cell or tissue can be obtained by metabolic profiling. In addition, they also can provide information on metabolites that are directly produced in response to endogenous and exogenous factors [14]. But, integrating proteomic, transcriptomics, and metabolomic information to provide a better understanding of cellular biology is still one of the challenges of systems biology and functional genomics. Within a few decades, metabolomics has been applied to various research fields, especially in the field of oncobiology. **Figure 1** summarizes the timeline of metabolomics development and application [13-16].

The Application of Metabolomics in Cancer

Metabolic reprogramming is a major phenomenon of cancer, and it is also an essential hallmark of cancer which facilitates tumorigenesis and malignant phenotype [17]. Cancer cells have been reported to support their rapid proliferation rates by high glycolysis, enriched phospholipid turnover, low mitochondrial activity, as well as decreased bio-energetic expenditure. Although changes in metabolic profiling are not specific to tumorigenesis, several kinds of tumor cells show a common characteristic, which is that tumor cells are able to escape death and immune invasion [18]. That is mean that metabolic changes are related to the shifted balance among growth, apoptosis and differentiation. Therefore, it can provide novel potential biomarkers for the detection and treatment monitoring of a variety diseases and response to therapeutic intervention [19,20]. It has been widely contributed to disease diagnosis, therapeutic monitoring, and pharmacodynamic evaluation [21-24]. Cancer metabolism has become a “hot spot” and is also gaining momentum for better mechanistic understanding of tumorigenesis. Therefore, metabolomics is a useful tool to investigate cancer from a novel perspective. Understanding the metabolic alterations of tumors remains an important undertaking, which will not only help study the mechanism of metabolic pathway in caner and promote the early detection of cancer, but also can predict the drug responsiveness contribute to development novel therapeutic strategy.

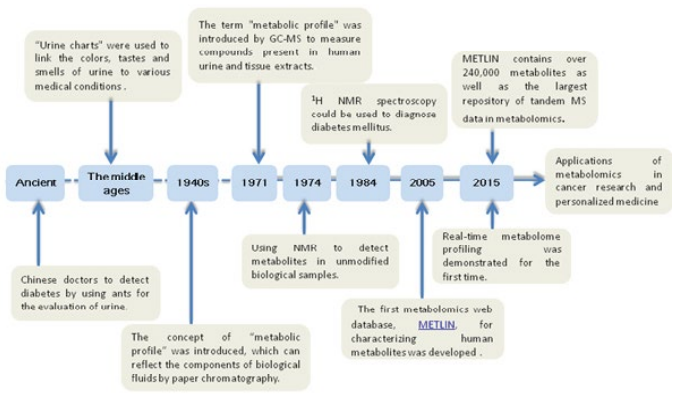

Figure 1 Timeline of metabolomics development and applications.

Metabolomics-driven target identification in metabolic pathway

Cancer cells exhibit a number of proposed common hallmarks, especially in altering nutrient uptake and utilization [25]. Metabolic alteration is thought to be essential for rapid cancer cell proliferation, but a systematic characterization of the metabolic pathways active in cancer cells is lacking, and what are their contributions remain unclear.

To systematically characterize cancer cell metabolism, researchers use the metabolomics to profile the major pathways of intermediary metabolism [26,27]. Metabolic profiling builds upon metabolic footprinting also known as exometabolomics (an analysis of extracellular metabolites profiling) and fingerprinting (an analysis of intracellular metabolites profiling), and provides a systematic and quantitative assessment of cellular metabolic activity and metabolites [28]. In addition, metabolic profiling helps the researchers to identify the key role for some substances in cancer cell proliferation and survival, and may provide a metabolic vulnerability for selectively targeting rapid cancer cell proliferation.

Jain et al. used the mass spectrometry to measure the consumption and release (CORE) of metabolites from the NCI-60 cancer cell lines, and integrated CORE profiles with a pre-existing atlas of gene expression. And then they identified glycine consumption and expression of the mitochondrial glycine biosynthetic pathway as strongly correlated with rates of proliferation across cancer cells. The proliferating cells were impaired rapidly by directly antagonizing glycine uptake through interference its mitochondrial biosynthesis. Moreover, higher expression of this pathway was associated with greater mortality in breast cancer patients [29]. Sellers et al. injected patients with early-stage

non–small-cell lung cancer (NSCLC) with uniformly 13C-labeled glucose before tissue resection. Then, after resection, they analyzed its intra-tumoural metabolic fate. The result showed that pyruvate carboxylase (PC) expression was greatly enhanced in cancerous tissues, whereas GLS1 expression showed no trend. PC is an anaplerotic enzyme that carboxylates pyruvate directly to oxaloacetate; hence its activity sustains TCA cycle metabolite levels. *Ex vivo* experiments comparing the metabolite labelling patterns of malignant and non-cancerous tissue slices from the same patients confirmed the *in vivo* results. In addition, genetic PC silencing in different NSCLC models exerted growth-inhibitory effects [30]. Hepatitis B virus X protein (HBx), a multifunctional onco-protein, was reported to be associated with HBV replication, DNA repair, cell-cycle progression, transcriptional regulation, and to play an essential role in HBV-related HCC [31]. Yue et al. showed that HBx disrupted the metabolism of glucose, lipids, and amino acids, especially nucleic acids through NMR-based metabolomic approach [32]. Finally, they also revealed that HBx initially caused DNA damage and then perturbed nucleic acid metabolism, which in turn blocked DNA repair and led to HCC. Based on combined analyses of 1H-NMR metabolomics and molecular biology technologies, Dai et al. confirmed that E4F1 (a cellular target of the E1A adenoviral oncoprotein, was reported to interact with HBx) may contribute to the proliferation of HBV-infected HCC cells by neutralizing the capacity of HBx to activate a p53-dependent metabolic and growth arrest phenotype [33].

Overall, these studies illustrated the majorly altered metabolites and corresponding metabolic pathways involved in stepwise carcinogenesis, suggesting that a metabolomics-based strategy for identification of driven targets for all kinds of cancer research or early diagnosis.

As the biomarker for diagnosis in cancer

The development of effective screening methods for early cancer detection is one of the foremost challenges facing modern cancer research. Metabolomics is the systematic study of small-molecular weight substances in cells, tissues and/or whole organisms, as influenced by multiple factors including genetics, diet, lifestyle and pharmaceutical interventions. These substances may directly or indirectly interact with molecular targets, and thereby influence the risk and complications associated with various diseases, including cancer [34]. Since the metabolites will be changed by exposing to an agent (drug or food component) or under the condition of certain disease, which is fundamental to understanding the metabolome and its potential use for predicting or diagnosing the disease in the early stage. By measuring the composition of small molecules in tissues, blood or urine, it provides a sensitive molecular readout often associated with disease and its states, especially in cancer **(Figure 2)**. Now, with the well-developed metabolomic technologies, more and more relevant metabolic biomarkers of tumors have been identified **(Table 1)**. Bowers et al. applied high performance liquid chromatography-mass spectrometry (HPLC-MS) methods to obtain serum metabolite profiles from patients with HCC (with underlying HCV) and HCV alone , illustrated that 5 characteristic metabolites were decreased in HCC patients and two additional metabolites were systematic increased between

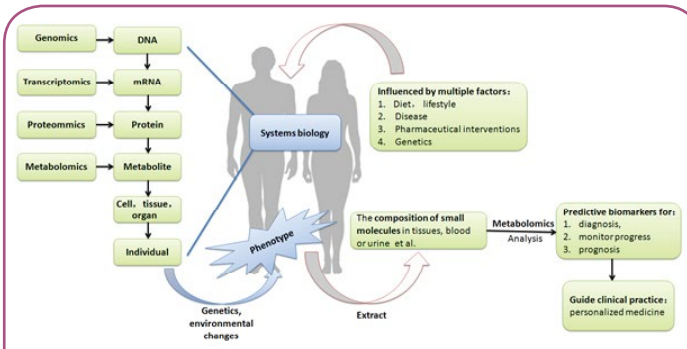

Figure 2 The outline of analytical metabolomics in patients.

HCC-HCV [35]. The results readily distinguish patients with HCC and HCV from those with HCV only. Differences in the metabolic profiles between high risk individuals and HCC indicated that it is a possibility to identify the early development of risk of liver cancer in patients. Fujimura et al. obtained the metabolic profiling based on liquid chromatography-mass spectrometry in both SUIT-2 and CAPAN-1 cells (responsiveness and resistance to gemcitabine, respectively), and then they identified that the glutamine and proline was decreased, but aspartate, hydroxyproline, creatine, and creatinine was increased. Their results suggested that metabolic profiling can isolate distinct features of pancreatic cancer in the metabolome of gemcitabine-sensitive and gemcitabine resistance cells. These findings may contribute to the biomarker discovery and an enhanced understanding of gemcitabine resistance in pancreatic cancer [36]. Manna et al. proved that the markers screen out by metabolomic profiles of urine and tissue samples from mice with colorectal tumors, which can predict mutant mice at risk of developing colorectal tumors with 100% accuracy even at 2 months of age when they present only few polyps. Further, they also performed metabolic profiling on colon tumor and adjacent non-tumor tissues from patients, and showed that 16 metabolites were significantly increased, which had stage-dependent. These urine and tissue markers might be used in early detection of colorectal cancer [37]. Koutros et al. used the metabolomic profiling to identify that the elevated levels of serum sarcosine are associated with an increased prostate cancer risk and sarcosine may be as an early biomarker [38]. The research of Plewa et al. identified histidine and citrulline as potential new ovarian cancer biomarkers. Furthermore, it also provided evidence that amino acids are involved in metabolic pathways related to tumor growth and play an important role in cancerogenesis [39].

Cancer biomarkers have become more and more apparent as containing useful information such as the possible cancer type and the stage of the patient's progression at a very early time. An ideal cancer biomarker should fulfill the following conditions: high sensitivity and specificity; absolutely reliable, possible and accurate; and should be able to reliably detect all cancers of the same type. And it should also be readily detectable in body fluids and tissue extracts with little trauma to the patient. Metabolic profiles may offer improved probabilities for translation of newly discovered biomarkers to clinical application. But, the successful clinical application of biomarker still has a long way ahead.

Table 1: Relevant metabolic biomarkers of cancer in human.

Associated tumors	Metabolite	Samples	Reference
Colorectal Tumors	Aspartic acid, glutamic acid, proline, threonine, lysine, arginine, uracil, xanthine, hypoxanthine, SAH, SAM, carnitine, SDMA, ADMA, betaine, and dimethylglycine was significantly elevated; L-alanine, glucuronoic lactone and L-glutamine (specific) was increased.	Tumors Serum	37 43
Lung cancer	Choline and linoleic acid was significantly decreased (defined as one combinational biomarker).	Serum	41
Breast cancer (IDC)	LPE was decreased and ceramide was increased.	Serum	42
Gastric cancer	3-HP was increased and pyruvic acid (specific) was reduced.	Serum	40
Pancreatic cancer	NAG, DMA, VLDL and acetone was elevated; 3-hydroxybutyrate, lactate, HDL, LDL, citrate, alanine, glutamate, glutamine, histidine, isoleucine, lysine, and valine were reduced.	Plasma	43
Ovarian cancer	Pseudouridine, N4-acetylcytidine, imidazol-5-yl-pyruvate, urate-3-ribonucleoside, 3-indolelactic acid, 3'-sialyllactose and 3-sialyl-N-acetyllactosamine was increased; L-histidine, N-acetylglutamine was reduced.	Urine	44
Prostate cancer	Arcosine was elevated; 1-SG was lower.	Serum Serum	38 45
Esophageal cancer	Malonic acid (specific) and L-serine was increased.	Serum	43

SAH: S-adenosylhomocysteine; SAM: S-adenosylmethionine; SDMA: Symmetric-dimethylarginine; ADMA: Asymmetric-dimethylarginine; 3-HP: 3-hydroxypropionic acid; IDC: Invasive ductal carcinoma; LPE: Lysophosphatidylethanolamine; NAG: N-acetyl glycoprotein; DMA: Dimethylamine; VLDL: Very low density lipoprotein; HDL: High density lipoprotein; LDL: Low density lipoprotein; 1-SG: 1-Stearoylglycerol.

Monitoring progress and prognosis in cancer

Early detection, close monitoring of disease progression in cancer can be critical for patient definite and good prognosis and treatment decisions. Efforts have been made to develop new and effective methods for improving early detection and patient monitoring, such as metabolomics. Now, metabolomics has been used in the identification of new biomarker for disease diagnosis. Moreover, it is considered that metabolomics would be a powerful tool to predict disease severity and drug responsiveness. Bannur et al. acquired the metabolomic profile from 21 ALL (Acute lymphoblastic leukemia) patients treated with 6-mercaptopurine, and 10 healthy volunteers. The results showed that 13 metabolites were significantly differently expressed in 19% of the patients who had relapses in their treatment. Their research contributes to identification of metabolites that could be used to monitor disease progress of patients and allow targeted therapy for ALL at different stages [40-46]. Zhu et al. applied a targeted liquid chromatography tandem mass spectrometry (LC-MS/MS) metabolic profiling and focused on sequential metabolite ratio analysis of serial serum samples to monitor disease progression from 20 colorectal cancer (CRC) patients. And they demonstrated that a panel of five core serum metabolites (succinate, N2, N2-dimethylguanosine, adenine, citraconic acid, and 1-methylguanosine) can be used for sensitive and specific CRC disease status monitoring. Their results suggested that the potential utility of metabolic profiling for CRC disease monitoring [47]. Recently, Xu et al. reported that they observed the acetyl phosphate formation in mammalian mitochondria using real-time in-organelle NMR metabolomics, and confirmed the positive regulation of mitochondrial PDH activity by p53 [48].

To investigate pharmacokinetic variability in abiraterone acetate metabolism, Bhatnagar et al. developed highly sensitive liquid chromatography/mass spectrometry (LC/MS) assays for the simultaneous quantitation of abiraterone and D4A in human plasma using high-resolution mass spectrometry (HRMS) on an Orbitrap mass spectrometer. Finally, they quantified the anticancer drug abiraterone and its metabolite Δ(4)-abiraterone in human plasma and demonstrated the inter-patient variability of up to 10-fold concentration [49]. Metabolomics is a promising technique that may lead to the identification and characterization of new disease fingerprints.

The Applications of Metabolomics in Development of Novel Therapeutic Strategy

More recently, there has been a resurgence of interest in targeting cancer metabolism due to the effective in inhibiting tumor growth, and it may also provide a therapeutic window [50-52]. Now, several metabolically targeted agents have been developed for pre-clinically or in clinical trials, including elevating reactive oxygen species (ROS) or block glycolysis, lipid synthesis, mitochondrial function, and glutamine synthesis pathways [53]. Although targeting cancer metabolism is a promising therapeutic strategy, successful treatment for cancer will depend on an accurate diagnostic identification of tumor subtypes with specific metabolic requirements.

The study of Jain et al. was the first to successfully identify metabolic subtypes through profiling of a large number of samples within one tissue type, and demonstrated that each subtype

is enriched for drug sensitivity to unique classes of metabolic inhibitors [54]. Daemen et al. successfully identified three highly distinct metabolic subtypes (Slow Proliferating, Glycolytic, and Lipogenic Subtype) in pancreatic ductal adenocarcinoma (PDAC) through broad metabolite profiling. Then they study the sensitivity to various metabolic inhibitors, and showed that the glycolytic subtype was enriched for lines that were sensitive to the LDHA inhibitor, oxamate and BPTES, whereas the lipogenic subtype was enriched for lines that were sensitive to inhibitors targeting lipid synthesis. Their data provided valuable predictive utility and thereby inform clinical evaluation of a variety of metabolic inhibitors such as MCT and glutaminase inhibitors currently undergoing phase I testing across a variety of tumor indications [55]. Metabolite profiling in classifying tumors to different subtypes is a pilot study, which might be a subtype-specific tool to predict cancer. For example, the different subtypes may help predict sensitivity of tumors to a variety of metabolic inhibitors which currently undergoing phase I testing. Liu et al. also showed B cell lymphoma cells rely more on glucose or glutamine have a stronger sensitivity to glycolysis or glutaminolysis inhibitor respectively [56]. The identification of distinct metabolic reprogramming events or metabolic subtypes in cancer may inform patient selection for investigational metabolic inhibitors and in the selection of new therapeutic targets. This may lead to potential new tools to increase efficacy of cancer therapy and provide a new approach for cancer therapy. Wu et al. screened out the 9-cis-Retinoic acid, an isomer of all-trans retinoic acid, can as a differential metabolite that significantly decreased during breast cancer progression to metastasis. And they also demonstrated that the knockdown of aldehyde dehydrogenase 1 family member A1, a regulatory enzyme for 9-cis-Retinoic acid, can remarkably impaired cell invasion and migration by preventing the key regulator cofilin from activation and inhibiting MMP2 and MMP9 expression. Their results revealed the potential inhibitory role for 9-cis-Retinoic acid in breast cancer progression by attenuating cell invasion and migration [57].

As such, it is important to determine the specific metabolic alterations in each particular cancer type so that effective cancer type specific metabolic intervention strategies can be developed. Furthermore, a combination of conventional chemotherapeutic agents and metabolic modulators may enhance therapeutic activity and should be further evaluated.

Limitations of Metabolomics in Cancer Research

Metabolomics has become a hot spot in the scientific community and better understanding of the complex pathophysiology of all kinds of cancer, but this discipline still lags behind other omics technologies to a great extent [58]. The most common challenge for metabolomics is its technical limitations. Now, a large number of small molecules (intermediary metabolism) can be detected and identified in a single run by metabolomics [59]. However, metabolomic data usually do not include all of the metabolites. In general, the information of metabolites, including the concentration and quality predicable, can be provided by mass spectrometry which are derived from mass peak intensities, and the peak intensities strictly rely on the samples themselves (the exact pH value) and the type of mass spectrometer used, and the technical characteristics, options and protocols applied (detector consumption, purity of the solutions used, the operating state of the ion source and ion transferring system) are also the influencing factors. Although the development of analytical instrumentation has made much progress, most metabolites cannot be detected due to their dramatic concentration range and great complexity, and these undetectable metabolites may also play an important role in living systems [8]. In addition, the type of database search employed is very important too. The significant challenge is using calibration curves to determine the concentration of unknown substances base, and how to convert mass peak intensities to actual concentration [60,61]. The limited database and analysis tools may lead to false-negative or false-positive results.

And now, a large number of small molecules (metabolites) can be detected in a single sample, including cell, tissue, bodily fluid samples et al. A great challenge exists in data analysis of metabolomics, which is the most time-consuming step of metabolomic studies. From these metabolites, we usually obtained several up-regulated and down-regulated metabolites. But, how to find out which up-regulated or down-regulated metabolites have biological role in cancer research is a huge problem surrounded by huge challenges. Because, the most changeable metabolites usually do not play the key role in the metabolic pathways of biological system, whereas the minor changes used to the real target of cancer development, progress and the therapeutic, which are easily overlooked. Just like that you're looking for a needle in a haystack. And the samples collection is also a challenge: frozen human normal and malignant tissues represent a valuable source for "omics" analysis in translational cancer research and molecular pathology. However, the success of molecular and cellular analysis depends strongly on the collection, handling and storage procedures, as well as quality control of fresh human tissue samples. Veneroni et al. also showed that UVS (under vacuum storage) can preserve tissue specimens for histological, transcriptomics, and proteomic examinations up to 48 hours and possibly longer, whereas, unfortunately, it has limitations for metabolomic applications [62]. And the last but not least, very different biomarkers can be screened out for the same cancer based on the different sample processing, analysis platform and data handling. All these are the obstacles to bring metabolomics into clinical application.

Future Perspectives for Metabolomics in Cancer Diagnosis and Therapy

Metabolomics is the link between genotypes and phenotypes. Metabolites, intermediary metabolism, being the end products are more stable than mRNAs and proteins, which may help us better understand the metabolic changes in tumors. Studies have shown the efficacy of metabolomics in identifying biomarkers associated with diagnosis, monitoring progress and prognosis, and treatment of cancer. The concept of precision medicine-prevention and treatment strategies that take individual variability into account is gradually gaining structure and strength

in cancer care. But the prospect of applying this concept broadly has been dramatically improved by the recent development of large-scale biologic databases (such as the human genome sequence), powerful methods for characterizing patients (such as proteomics, metabolomics, genomics, diverse cellular assays, and even mobile health technology), and computational tools for analyzing large sets of data [63]. In addition, personalized medicine strongly emphasizes the use of predictive biomarkers, which may make easier to integrate the metabolomics into clinical patient management.

Besides discovering and identifying metabolic biomarkers that will enable better diagnosis and therapy monitoring, we expect new and broad research programs of metabolomics to provide new molecular targets and enable tailoring of treatments to precision medicine. Actively low cost and reproducible metabolomics analyses, combined with other "omics" approaches (proteomics, genomics, diverse cellular assays, etc.), may soon develop modern medicine. So, despite obvious obstacles, the increasing use of metabolomics in clinical research may soon turn it into an extremely powerful tool used to evaluate and monitor the occurrence, progress and prognosis of cancer, and ultimately use them to build the evidence base needed to guide treatment decision [64,65].

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