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Research Article

METABOLOMICS IN CANCER: TECHNIQUES, BIOMARKERS, DRUG THERAPY AND GLUCOSE METABOLISM

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Abstract

Carcinoma is a devastating illness that alters cellular metabolism and its surrounding environment. Metabolomics has the potential to detect hundreds to thousands of metabolites in biofluids and tissues that contain them; it is a fast evolving and very successful approach. Thanks to new metabolomics tools, researchers have been able to delve deeper into cancer metabolism and learn more about how cancer cells take advantage of glycolysis, or the "Warburg effect," to make lipids, amino acids, and nucleotides essential building blocks for tumour growth and vascularization. Metabolomics research is currently being used for a variety of purposes, such as discovering diagnostic biomarkers for cancer in the clinic, understanding the complex heterogeneous nature of cancer better, discovering pathways involved in cancer that could be utilised as new targets, and monitoring metabolic biomarkers during therapeutic intervention. Metabolomic analysis of various metabolic profiles is a powerful and technically feasible tool that can be used to track the evolution of cancer metabolism and treatment response as the disease progresses. To date, a plethora of original research has highlighted the potential of metabolomics in several areas of research concerning tumour metabolic reprogramming. By providing valuable information on the cancer patient's reaction to medicinal procedures, these metabolomics methods may also offer hints to customised cancer treatments. Metabolomics provides the means to obtain this data. The aim of this work is to offer a brief overview of how metabolomic methods can clarify the effects of changes on the metabolic profile of a tumor.

Keywords: Cancer: Techniques, Biomarkers, Drug Therapy, Glucose Metabolism.

INTRODUCTION

In recent years, there has been a growing interest in the connection between metabolism and tumors. This is due to the fact that metabolism serves as a key link between environmental factors, metabolic small molecules, host genes, and illnesses. There is a process of evolution that takes place within the tumour itself as a result of environmental selection pressures that are produced by genetic and microenvironmental variables. It is referred to as metabolic reprogramming and occurs simultaneously when the metabolic properties of the tumor undergo adaptive changes [1, 2]. These changes are controlled by the genotypes of the tumour. Several studies have demonstrated that the microenvironment surrounding a tumour frequently lacks essential nutrients. As a result, tumour cells are able to reprogramme their metabolism as well as the metabolism of the microenvironment in order to preserve their capacity for proliferation. One of the newest omics technologies is metabolomics. It employs state-of-the-art analytical equipment in combination with pattern recognition methods to track and identify patients' metabolic changes in relation to the state of a disease or in reaction to a medical or external intervention. Changes in environmental factors, genetic variation and regulation, gut microbiota, enzyme levels and kinetics, and other factors all contribute to altered global metabolomics. Consequently, alterations in metabolomics point to shifts in molecular physiology and phenotype [3]. To evaluate the efficacy of medicinal treatments for cancer, as well as to identify the biomarkers and metabolic pathways that are changed in cancer, metabolomics and other omic technologies are presently being used [4].

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Metabolomics may prove to be an invaluable tool in the fight against cancer, both in terms of early detection and diagnosis and the assessment of therapeutic interventions, since the disease is recognised to impact cellular metabolism [5]. When aerobic glycolysis increases in cancer patients, a phenomenon known as the "Warburg effect" is attributed to it. Metabolic has been able to delve considerably deeper into cancer metabolism thanks to new analytical tools and statistical capacities. Metabolomics has been able to shed light on how cancer cells exploit glycolysis for their own benefit, allowing them to manufacture lipids, amino acids, and nucleotides—essential components for tumour growth and vascularization [6]. Metabolomics and metabolomics are two terms that describe the study of metabolic profiles on a global scale. The field of metabolomics studies the observable metabolite pool in living organisms in response to pathophysiological stimuli or genetic manipulation, while the field of metabonomics studies the "quantitative measurement of the dynamic multiparametric metabolic response of living systems to pathophysiological stimuli or genetic modification" [7]. You will hear each of these words used equally. The pool of metabolites found in biofluids and tissues at any given moment is impacted by a number of lifestyle factors, including genetic variables, food, medications, exercise, gut microbiota, health-to-disease status, hormonal balance, and age [8]. The quantitative analysis of a group of metabolites linked to a particular pathway is usually what people mean when they speak about metabolic profiling [9]. The evaluation of lipid profiles is the focus of the specialised subfield of metabolomics known as lipidomics. Lipids are involved in a number of key processes that are associated with cancer, including invasion, migration and proliferation [10]. Another subfield within the discipline of metabolomics concerns the use of labeled substrates, such as

13C-labeled glucose, for the purpose of defining metabolic fluxes or biomarkers in disease states. We can learn more about the role of metabolism in disease or treatment responses by monitoring the conversion of labeled substrates to products of their pathway at time intervals using this method. For example, glycolysis can convert glucose to lactate, while the pentose phosphate pathway can redirect it to ribose. There is a way to tell how much glucose goes through each pathway by looking at the 13C labeled carbons in the glucose. Thanks to these data, metabolic phenotypes in disease states [11] or drug response can be defined, leading to a better understanding of the pathways that are upregulated or downregulated. So, to comprehend cancer and the effect of medical treatment on patients, glucose flux technology is ideal [12]. This is because glycolysis is involved in cancer development to a considerable extent. Finding cancer-specific biomarkers that can be utilised for diagnostic, prognostic, or predictive purposes for patients is the end goal of most metabolomics cancer research. A biomarker is a "characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or biological responses to a therapeutic intervention" [13], according to the Food and Drug Administration (FDA). In order to learn more about the illness under study, researchers use biomarkers. Any measurable component (gene, protein, metabolite, heart rate, tumour size, etc.) that suggests a particular condition to patients is called a diagnostic biomarker. Differentiating between prognostic and predictive biomarkers, we find that the former determines the patient's risk of disease occurrence or progression and the latter indicates the likelihood that a patient will respond to a particular medical treatment [14].

Metabolomics techniques

The assessment of the dynamic multiparameter metabolic response of biological systems to a variety of stimuli and genetic alterations in specified quantities is what is meant by the term "metabolomics techniques," according to the published definition [15]. In most cases, they are utilised as a beneficial method for identifying biomarkers [16], and their primary focus is on conducting examinations of metabolites in biological fluids, cells, and tissues. Measurement of metabolites through the use of high-throughput and high-resolution detection technology, acquisition of enormous datasets, acquisition of various metabolites through data analysis, identification of metabolic pathways, and explanation of the biological importance of these metabolites are all components of the elementary research methodology. Nuclear magnetic resonance (NMR), liquid chromatography-mass spectrometry (LC-MS), and gas chromatography-mass spectrometry (GC-MS) are the three techniques that are typically utilised in the field of metabolomics.

Biomarkers of Cancer

It has been demonstrated through the use of metabolomics on cancer tissue samples that altered cellular metabolism is a feature of virtually all various kinds of cancer [17]. There is no correlation between the exact organ location of the tumour and this phenomenon. Cancer is a complicated disease state that transforms normal, healthy cells into tumour cells. Cancer cells primarily use glucose and glutamate to generate energy for themselves, as well as to synthesise carbohydrates, fatty acids, amino acids, and nucleotides, which are essential for the production of proteins and the proliferation of cells [18]. Numerous medications that have been created for the purpose of cancer chemotherapy have focused their attention primarily on the altered metabolic pathways that are present in cancer. As a result, metabolomics can be utilised to identify altered metabolic pathways in cancer, and it also has the potential to be beneficial for monitoring cancer medication therapy that targets the altered metabolic pathways. The use of metabolomics in conjunction with conventional histological examinations of biopsies has been scrutinised, and it has been demonstrated that numerous metabolites exhibit a correlation with the aggressiveness of cancer disease [19, 20]. The discovery of metabolic biomarkers or patterns of cancer has been one of the most significant areas of research in the field of metabolomics. Due to the fact that it is common practice to get a biopsy of cancer tissue and biofluids from cancer patients, metabolomics research has found a fertile ground in the field of cancer. Around the same time, non-cancerous tissue from the surrounding area is occasionally collected. A wide variety of samples, in addition to tissue, have been utilised in metabolomics research on cancer. These samples include serum [21, 22], plasma, saliva, urine, and breath. The goal of these investigations is to identify characteristics that are indicative of cancer. In a pilot study that was quite modest, serum metabolomics was also utilised to determine the stage of pancreatic cancer [23].

Metabolomics techniques based on nuclear magnetic resonance (NMR) and mass spectrometry (MS) can be used to examine water- or polar-based extracts of cancerous and adjacent tissues. Nuclear magnetic resonance (NMR) methods known as "high resolution magic angle spinning" (HR MAS) can be used to analyse cancer tissue samples if they are accessible [24]. Cancer research has made extensive use of metabolomics techniques, many of which are based on nuclear magnetic resonance (NMR) and mass spectrometry (MS). The "Warburg" effect is the general idea that glycolysis increases in cancer patients. Thanks to something called the "Warburg effect," cancer cells can bring glucose in for glycolysis [86]. A growing amount of evidence indicates that glycolysis is likely an adaptation to the hypoxic environment of the tumour cell, even if its principal role is to provide energy to the cancer cell [69]. The metabolites produced by glycolysis are also essential for the growth of cancer cells, giving them a considerable growth advantage [24, 25].

Measuring Metabolic Health Indicators

Various in vivo imaging modalities have been used in cancer diagnosis, including X-ray, positron emission tomography (PET), single-photon emission computed tomography (SPECT), MRI, MRSI, and ultrasound [26]. One functional imaging method that takes advantage of the fact that cancer cells absorb glucose at a higher rate than normal cells is positron emission tomography (PET). Positron emission tomography (PET) can detect glucose uptake by cancer cells using 2-[18F] fluoro-2-deoxy-D-glucose (FDG), a radiolabeled glucose analog [27]. Both magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRSI) have been used to diagnose and evaluate the treatment of a wide variety of cancers in a non-invasive manner. It is common practice to use contrast agents in dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) to improve image quality for diagnostic purposes [28, 29]. When it comes to detecting problems related to oncology, diffusion-weighted magnetic resonance imaging (MRI) provides information that is

complementary to that of standard MRI. This is because it analyzes the migration of water in the tissue. When it comes to breast cancer diagnosis, magnetic resonance imaging (MRI) is often used in conjunction with mammography because it is much more accurate and sensitive than mammography alone [31, 32]. A technique known as MRSI is used to obtain an NMR spectrum from a small three-dimensional voxel located in the tissue. Standard magnetic resonance imaging (MRI) provides a number of advantages over MRSI, including the ability to identify a wide range of metabolic changes in tumors, in addition to glucose uptake. Additionally, MRSI is superior to MRI, which can only detect water density or water movement. In comparison to MRI, MRSI has a number of drawbacks, including significantly longer acquisition periods, a more difficult data processing technique, and a lack of familiarity with practicing doctors. Monitoring and diagnosis of breast [33], brain, and prostate cancers have all been accomplished by the use of MRSI detection of choline.

The MRSI detection of choline has been shown to have a sensitivity of one hundred percent for the detection of malignant breast tumours as opposed to benign breast tumours, and it has the potential to reduce the requirement for breast biopsies that are not essential [34, 35]. In order to successfully classify nine distinct forms of brain cancer, it has been demonstrated that single voxel MRSI data can be considered successful [36]. Data normalisation, re-calibration of the spectra to specific peaks, weighting of the data, and re-normalization of the MRSI spectral data were the four phases that Alusta and his colleagues proceeded through in order to handle the MRSI data before constructing a classification model. The accuracy of predicting nine distinct kinds of brain cancer increased from 31% to 95% as a result of the four-step data processing [37].

Metabolomics and Cancer Drug Therapy

Chemicals that were referred to as "antimetabolites" at the time were utilised in the initial medicinal treatments for cancer [38]. These substances were given the label antimetabolites due to the fact that they were chemically comparable to endogenous metabolites in certain pathways and that they disrupted the regular metabolic processes that occurred within those pathways. Methotrexate, cytarabine, and 5-fluorouracil are all examples of antimetabolites that directed their attention towards the late stage of DNA synthesis. Within the context of cancer treatment, there is a significant amount of interest in targeting altered cancer metabolism as a therapeutic strategy [39]. One of the targets of cancer therapy is the process of de novo fatty acid synthesis. The enzyme fatty acid synthase (FASN) is targeted by the medicine Orlistat and several other drugs. Other cancer drugs, on the other hand, target ATP citrate lyase (ACLY). The glycolysis enzyme known as hexokinase (HK) is the target of the medications lonidamine, 2-deoxyglucose, and 3-bromopyruvate that are currently in the process of being developed. Another treatment that is currently in the process of being developed targets pyruvate kinase (PK). Each of these medications ought to be able to suppress glycolysis, which is a process that is recognised to be elevated in cancer. It is hoped that cancer medications that inhibit enzymes that are elevated in cancer cells may lower endogenous metabolites that are required for the growth of cancer, hence limiting the proliferation of cancer cells and possibly reducing transformation in pre-cancer cells. It is expected that the levels of endogenous metabolites will begin to change prior to the reduction in size of the tumour, which is a typical clinical end point for cancer treatment. The medication phloretin targets the glucose transporter (GLUT) and the monocarboxylate transporter (MCT), which are both examples of transporters that are targets for cancer therapy. The Na+/H+ exchanger (NHE1) is the target of cariporide, which is a medication that is currently in preclinical development. There are several more treatments that are currently in clinical development that target MCT molecules. When compared to other omics, metabolomics is the most suitable method for determining whether or not these cancer treatments ultimately create changes to metabolic pathways. Additionally, it is able to detect drug pharmacokinetics.

Healthy people reacted differently than cancer patients treated themselves, according to Weiss's [40] description of a hypothetical pharmacometabolomics study. Also, cancer patients taking Raf inhibitors compared to those taking endothelial growth factor inhibitors had different metabolic profiles. Human breast cells treated with docetaxel were studied using pharmacometabolomics, and the results showed that the metabolism of glutathione and phospholipids responded both time- and dose-dependently. Clinical pharmacometabonomics studies have shown a correlation between lipid levels and the severity of toxicity in capecitabine-treated patients with inoperable colorectal cancer; higher lipid levels were associated with more severe outcomes. To determine if the metabolic response is associated with cancer grade, adverse events, and tumour growth or shrinkage, it will be crucial to integrate genetics, microRNA, mRNA, and imaging data with these pharmacometabolomics clinical cancer studies in the future. A lot of people are interested in using metabolomics for cancer detection, cancer prognosis, and cancer therapy management because pharmacometabolomics can track how drugs alter patients' metabolic reactions.

Glucose Metabolism

As a result of the requirement for malignant proliferation, tumour cells display a phenomena known as the Warburg effect, which is characterised by fast glycolysis in a variety of setting conditions. Because tumour cells have a high capacity for proliferation and a high need for energy, the local tissue microenvironment frequently becomes deficient in oxygen due to the presence of tumour cells. The process of glycolysis is 100 times faster than aerobic respiration and delivers the amino acids and intermediate metabolites of pentose phosphate that are necessary for highly multiplying cancer cells [41]. Although glycolysis is not as efficient as aerobic respiration in terms of the provision of energy, it is 100 times faster than these processes. Therefore, cancer cells become less efficient at using the mitochondrial aerobic oxidation pathway for energy, or perhaps stop using it altogether, in favour of the glucose glycolysis pathway, which results in the production of a significant amount of lactic acid. The Warburg phenotype is characterised by a number of metabolic characteristics, one of which is aerobic glycolysis. This metabolic feature is brought about by active metabolic reprogramming, which is necessary for the maintenance of cancer cell proliferation and the advancement of malignant disease. Glycolysis is just one of the routes that are included in glucose metabolism; there are several other pathways that require glucose. The pentose phosphate route (PPP), the hexosamine pathway, and glycogenesis are considered to be among these pathways [41].

Table 1. FT-IR peak values of solid analysis of *Brassica oleracea.*

No.	Peak (Wave number cm-1)	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area	Type of Intensity	Bond	Type of Vibration	Functional group assignment	Group frequency
1.	667.37	70.282	2.383	667.01	661.58	2.226	0.080	Strong	=C–H	Bending	Alkenes	650-1000
2.	690.52	71.720	0.518	713.66	686.66	3.769	0.059	Strong	=C–H	Bending	Alkenes	650-1000
3.	788.89	77.439	2.341	821.68	775.38	4.707	0.357	Strong	=C–H	Bending	Alkenes	650-1000
4.	999.13	66.259	1.402	1006.84	898.83	12.823	0.220	Strong	=C–H	Bending	Alkenes	650-1000
5.	1029.99	63.849	0.209	1031.92	1008.77	4.297	0.003	Strong	C-F	Stretch	alkyl halides	1000-1400
6.	1226.73	82.894	0.214	1228.66	1190.08	2.659	0.001	Strong	C-F	Stretch	alkyl halides	1000-1400
7.	1417.68	85.533	0.939	1427.32	1390.68	2.347	0.088	Strong	C-F	Stretch	alkyl halides	1000-1400
8.	1454.33	85.135	1.371	1483.26	1448.54	2.052	0.147	Strong	C-F	Stretch	alkyl halides	1000-1400
9.	1516.05	85.999	0.843	1521.84	1485.19	1.943	0.041	Medium	C=C	Stretch	Aromatic	1400-1600
10.	1539.20	85.109	1.482	1571.99	1529.55	2.655	0.167	Medium	C=C	Stretch	Aromatic	1400-1600
11.	1645.28	78.585	0.511	1647.21	1579.70	5.122	0.113	Bending	N-H	Stretch	Amide	1550-1640
12.	2854.65	85.991	4.453	2868.15	2816.07	2.326	0.326	Strong	C-H	Stretch	Alkane	2850-3000
13.	2924.09	81.181	9.343	2989.66	2879.72	6.487	1.847	Strong	C-H	Stretch	Alkane	2850-3000

Table 2. FT-IR peak values of solid analysis of *Celosia argentea* .

No.	Peak (Wave number cm-1)	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area	Type of Intensity	Bond	Type of Vibration	Functional group assignment	Group frequency
1.	1020.34	75.578	0.326	1022.27	918.12	8.672	0.083	Strong	C-F	Stretch	alkyl halides	1000-1400
2.	1238.30	87.413	2.075	1276.88	1209.37	3.615	0.346	Strong	C-F	Stretch	alkyl halides	1000-1400
3.	1317.38	86.158	2.800	1342.46	1288.45	3.054	0.316	Strong	C-F	Stretch	alkyl halides	1000-1400
4.	1608.63	84.616	0.464	1612.49	1579.70	2.126	0.060	Bending	N-H	Stretch	Amide	1550-1640
5.	2918.30	88.087	5.180	2951.09	2877.79	2.854	0.656	Strong	C-H	Stretch	Alkane	2850-3000

All of them undergo reprogramming within cancer cells, and this reprogramming can be utilised to selectively target cancer cells by targeting them. It has been discovered that the microenvironment of the tumour as well as a number of signalling pathways that promote cancer greatly upregulate the glycolysis process. This provides a wide range of possible targets for suppressing glycolysis in the context of tumour therapy. This has been demonstrated to be the case in a number of different tumour situations, and it is linked to unfavourable outcomes for tumours.

Lipid Metabolic

The multiplication of tumour cells requires a significant amount of energy, which is provided by lipids. This energy is necessary for the maintenance of membrane synthesis and other tasks associated to tumour cell growth. There is a correlation between the systemic metabolic changes that are associated with higher consumption of saturated fat and obesity and an increased risk of prostate cancer development and mortality. In primary prostate cancer, studies have demonstrated that the consumption of saturated fats in the diet helps to the growth of the tumour by imitating the overexpression of MYC. This suggests that therapeutic techniques that involve adjustments to the diet could be effective in treating the disease [42]. Information on lipid alterations in a variety of tumour cells can be obtained through the use of lipid metabolomics approaches.

Amino Acid Metabolism

The emergence of gastric cancer is associated with alterations in the amino acid metabolic spectrum, and the amino acid metabolic route is abnormal in patients with gastric cancer. This is demonstrated by the substantial link that exists between the levels of alanine and arginine and the T stage of the cancer. In order to take part in the tricarboxylic acid (TCA) cycle, glutamine is capable of completing the synthesis of a wide range of other amino acids. Further evidence reveals that glutamine is the driving force behind the glucose-independent TCA cycle [43]. The reason behind this is that when glucose levels are low, glutamine produces significantly more fumarate, malate, and citrate. An increase in glutamine, a key component for bioenergy production depending on mitochondria and cell biosynthesis, is a prominent feature in many cancer cells. The metabolic profiles of gastric cancer (GC) and gastric ulcer (GU) were compared using LC-MS-based plasma metabolic studies. It was found that GC patients had higher plasma ornithine levels compared to GU patients, but GC patients had lower plasma glutamine, histidine, arginine, and tryptophan levels. This was found in a study that evaluated the metabolic profiles of people with GC and GU.

Conclusion

Ongoing monitoring of the dynamics of tumour metabolism and response to treatment can be accomplished through the utilisation of metabolomics techniques throughout the course

of the disease. An additional area that is becoming increasingly significant is the identification of biomarkers for the purpose of developing personalised treatment regimens. At the same time, metabolomics analysis may also result in the discovery of new pharmacodynamic biomarkers and the monitoring of drug resistance in the tumour. In addition, it may provide clinical information that is more accurate and helpful on the metabolic requirements of the tumour. Cancer is a disease that results in changes to the metabolic processes of a cell, and metabolomics techniques are currently being utilised in order to get a deeper comprehension of these alterations in cancer metabolism. yet, first results are still experimental, and it needs to overcome numerous hurdles in order to be completely applied and realise its full potential. Metabolomics has showed a lot of promise for personalised medicine and cancer diagnoses; yet, it is still in the experimental stage. Some of the challenges that need to be addressed include: establishing universally accepted quality control standards; conducting validation studies; distinguishing between radiation damage and drug adverse events; enhancing metabolomics with clinical metadata; storing and interpreting clinical metabolomics data; sharing this data with regulatory agencies; and finally, introducing NMR spectrometers and MS into a clinical setting. Metabolomics, when combined with other systems biology datasets, will allow us to better understand the complexities of cancer and find individual responses to treatment. Numerous cancer medicine therapy are now under development, mostly as a result of the altered metabolism that happens in tumours. The altered metabolic pathways and the associated enzymes or transporters are the targets of these cancer-related medications. In order to better understand the complex nature of cancer and to inform clinicians about the patient's reaction to medical interventions for cancer, metabolomics analyses of cancer patients' tissue biopsies and biofluids will remain valuable. Metabolomics databases that help doctors understand the results of metabolomics and standardised and certified quality standards are still necessary for metabolomics to be successful and extensively used in the therapeutic setting.

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