Using Metabolomics to Find Cancer Biomarkers and DevelopTargeted Therapies

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ABSTRACT

One of the most common causes of mortality worldwide is cancer. When it comes to early cancer detection and diagnosis, metabolomics, an omics science that focuses on small molecules metabolites within biological systems, is a powerful tool that can identify hundreds to thousands of metabolites in biological fluids and tissues. It also serves as a predictive and pharmacodynamics marker of drug effects. Cancer is a deadly disease that is on the rise and affects cellular metabolism. In order to better understand how cancer cells employ metabolism, new developments in metabolomics techniques have made it possible. The "Warburg Effect" of glycolysis is used to create lipids, nucleotides, and amino acids that are beneficial for tumor growth and vascularization. Metablomics is currently being used to identify diagnostic biomarkers in clinical and laboratory settings in order to study the metabolic pathways of cancer cells that may serve as novel targets for endogenous biomarkers. These metabolic pathways for cancer track and forecast metabolic biomarkers for cancer treatment and long-term outlooks. Here, we will examine the existing and future uses of metabolomics for biomarker-based cancer diagnosis. By using NMR, LC/MS, and GC/MS techniques on cancer patients, we will conduct a sample research. We will talk about how robotic pills and metabolomics gives clinicians important information about cancer patients so they can develop individualized cancer treatments. In order to pinpoint the pathways implicated in cancer metabolism, we will use data analysis and bioinformatics technologies.

1. INTRODUCTION

Cancer is a life threating disease and it very difficult to detect it in early stages. Despite aggressive treatment of cancer patients have less than five years survival time (Zoli *et al*.,1996). According to a 2020 report of the World Health Organization (WHO), there were approximately 18 million new cancer cases and 10 million deaths occurred worldwide (Shayan, N. A. *et al.*, 2023). The leading cause of cancer-related deaths worldwide is lung cancer. The 5-year survival rate for lung cancer is only 21%, even though recent developments in precision medicines (such as next-generation sequencing, targeted therapy, and immunotherapy) have significantly improved the therapeutic response (Yang, C. Y. *et al*., 2023).

Treatment for early-stage lung cancer has also changed, with surgical resection now being the preferred method for non-small-cell lung cancer (NSCLC) patients in stages I–II. Additionally, perioperative chemotherapy and minimally invasive procedures have been linked to better patient outcomes. The expanding importance of precision medicine in the treatment of lung cancer is highlighted by biomarker research examining targeted treatments, ALK inhibitors, and immunotherapy for various patient subgroups (Hirsch, F. R. *et al*., 2017).

Targeted medicines, such as monoclonal antibodies and small molecule inhibitors, have fundamentally altered the way that cancer is treated. These medications are currently a part of the treatment for many common cancers, such as lymphoma, leukemia, multiple myeloma, breast, colorectal, lung, and pancreatic cancers. Targeted treatments have different modes of action and toxicity than conventional cytotoxic chemotherapy (Gerber, David E. 2008).

Despite advances in medical technology, some illnesses, like cancer, remain incurable. This is mostly because conventional anti-cancer treatments are ineffective and frequently have negative side effects on healthy cells. Getting accurate medicine delivery to tumor cells is a major obstacle in the fight against cancer. There has been an increase in interest in studying drug delivery systems

based on stimuli-responsive hydrogels that can control drug release from micro-structures in orderto address these problems and lessen adverse effects (Li, H., *et al*., 2016).

It is possible for hydrogels to contain up to 90% water by mass, which allows for significant volume variations. Hydrogels can also expand and contract more than tenfold in reaction to changesin their water content. Because of their biodegradable and biocompatible stimuli-responsive qualities, they have a wide range of applications in biomedical fields, including micro-robots, micro-grippers, drug-delivery systems, and actuators. These applications span a broad range of technological advancements, such as hydrogel-controlled thermally responsive materials, electroactive hydrogel actuators, light-driven composite actuators, magnetic hydrogel nanocomposites for remote drug release, electromagnetically actuated micro-grippers and micro- robots, electricity-powered hydrogel walkers, electronically programmable shape-changing hydrogels, smart bilayer actuators, and micro-sensors sensitive to pH fluctuations.

Metabolomics is a relatively new field in cancer research, various aspects of cancer metabolism have been investigated for a long time to understand a basic metabolism in tumors. The areas of cancer metabolism that have drawn the greatest interest include central carbon metabolism and the interaction between glycolysis, the TCA cycle, and oxidative phosphorylation. According to one theory, even under aerobic conditions, cancer cells preferentially convert pyruvate to lactate rather than blocking the TCA cycle. Even though it has now been demonstrated that there is no particular rule for cancer metabolism, it is still widely accepted that tumors exhibit increased glycolytic activity as well as decreased TCA cycle and oxidative phosphorylation activity. Otto Warburg first proposed this in 1956, and it is known as the Warburg effect. According to this hypothesis, tumor cells develop from healthy cells in two phases as a result of an irreparable injury to fermentation energy and respiration energy. Additionally, the Warburg effect suggests that cancer cells have increased glucose uptake (Warburg, 1956).

The most recent omics technology, known as metabolicomics, is used to track and identify metabolic changes in patients associated to disease and their response to medicinal therapies. Consequently, metabolomics reflect changes in molecular physiology and phenotypic modifications (Fiehn, 2002).

The detection of metabolic and biomarkers changed in cancer is presently done using metabolomics (Griffin *et al.*, 2004). Metabolomics is being utilized to assess cancer treatment. Cellular metabolism can change as a result of diseases like cancer. Cancer diagnosis and early detection can both benefit greatly from the use of metabolomics (Gowda, G. N, *et.al.*, 2008).

The "Warburg Effect" refers to the well-documented increase in aerobic glycolysis in cancer (Warburg, 1956). Recent developments in analytical technology have revealed how cancer cells use glycolysis to promote tumor growth and vascularization (Siemann, D. W. 2011). Metabolomics provides the ability to quickly examine tissues and biofluids, which has the potential to have a significant impact on clinical health practice. Information about patient profiles and the metabolic pool under certain settings are both provided by metabolomics (Fiehn, 2002).

Metabonomics refers to quantitative measurements of metabolism of living systems. The range of metabolites found in bodily fluids is influenced by lifestyle factors such as nutrition, activity, medication, endocrine state, and age (Lin, C. Y. *et.al*., 2006). The use of labeled substrate (13C-labeled glucose) to express biomarkers under illness conditions is the subject of another subclass in the metabolomics research. With the use of this technique, we can comprehend how diseases affect the labeled substrate's metabolism over the course of specific time periods. For instance, glucose can be subjected to glycolysis to produce lactate or diverted through the pentose phosphate pathway to produce ribose. Glucose's 13C-labeled carbons can anticipate and show how much of it travels through each pathway. As a result, the numbers give us more details about each of the metabolic pathways that are involved in cancer (Boros *et al.*, 2003) or drug response (Beger, 2013).

Glucose flux technology is ideal for researching cancer and patient responses to medications used for treating cancer because Glycolysis plays a significant part in cancer (Boros *et al* 2003).

The majority of metabolomics cancer research ultimately aim to find individuals with a cancer-specific diagnostic biomarker. Simply a reaction to therapeutic inventions is what the Food and Drug Administration (FDA) defines as "characteristics that is objectively measured and evaluated as an indicator of normal biological processes". A diagnostic marker, in its simplest form, is something that can detect gene, protein, and tumor size and subsequently reveal the presence of specific diseases in patients. Prognostic biomarkers can quantify and identify illness risk, whereas predictive biomarkers measure the traits that indicate whether or not a patient will respond to a specific medication (Beger, 2013).

This research proposal focuses on metabolomics methods for assessing metabolomes, metabolomics procedures for finding biomarkers in cancer studies, and metabolomics research in the field of cancer in the future.

1.1. METABOLOMICS

A biological system's endogenous metabolites can be evaluated using the omics discipline of metabolomics on a global scale. In essence, it is an analytical tool used in bioinformatics and other methodologies to find metabolites and their changes in biofluid (Spratlin 2009).

The process of metabolism, which is the culmination of all artificial reactions that happen within a cell or in an organism, is a branch of biochemical study that makes use of useful experimental fields. An emerging method in organic fields is metabolomics. Metabolomics has been widely utilized as a unique and diagnostic technique in clinical and medical studies as a result of novel and ongoing development in state-of-the-art medical studies and in Bioinformatics (Bujak, 2014).

2. METABOLOME

Metabolomes are essentially the entire amount of metabolites present within an organism, cell, or tissue. They are low molecular weight substances (about <1500 Da) complicated in the thorough absorption of cells and too difficult in communicating between these cells. Because metabolites are the end products of the genome and represent all of the information of a biological system, metabolome research is crucial for identifying biomarkers. Therefore, even when there are no discernible changes in the verbalization of proteins or transcripts, the alterations in metabolite aggregation are tagged and then exacerbated. There have only been 28 metabolites found so far. (Dunn *et al.*, 2008).

3. METABOLIC FINGERPRINTING:

The "finger print" of the metabolic configurations that most precisely reflect the detached phenotype may be provided by metabolomics (Zhao *et al.*, 2012).

Metabolic fingerprinting, which consists of a distinctive pattern identifying an image of the absorption in a particular cell line or tissue, is extremely useful in the identification and diagnosis of biomarkers (Zhang, 2012).

4. CANCER METABOLISM

One of the worst illnesses affecting people, cancer claims a staggering number of lives each year across the globe. One of the major areas of study in the biological sciences is cancer research, and despite extensive study, much more has to be learned about how cancer works. It is generally known that the metabolism of cancerous tissue differs from that of normal tissue, and a significant theory put forth by Warburg in 1956 stated that the anaerobic metabolism of cancer cells is essential for their growth. After this, cancer affects a variety of metabolic systems, and many more are continuously being discovered (Armitage, 2014).

5. CANCER METABOLISM-THE WARBURG EFFECT TODAY

Warburg first examined the energy metabolism in cysts using slices of living tissue in 1923 and found a distinctive metabolic pattern in malignancies (Holmes, 1991).

Warburg came to the conclusion that cancer cells engaged in lactic acid effervescence in aerobic settings. Warburg noted the greater lactate generation rate in malignancies. Additionally, tumor masses showed an insufficient blood supply of oxygen and glucose (Warburg et al., 1927). All of these findings supported Warburg's hypothesis that cancer cells develop as a result of irreversible damage to the respiratory system (Warburg, 1929).

5.1. Cancer bioenergetics-integeration of metabolism:

The utilization of carbon sources other than glucose was the subject of many investigations. Malignant transformation has also been connected to variations in protein expression (Richordson et al., 2008; Remple et al., 1994). There has been extensive metabolomic research to correctly characterize metabolomic bioenergetics. In actuality, some tumors are less affected by glycolytic control (Zemora *et al.*, 1996).

Lactate does not always come from fermentation because the cell can also get it from alanine transamination or glutamine-derived malate conversion (Frezza and Gottlieb, 2009). The importance of these pathways has led to the adoption of a variety of spectroscopic techniques, including mass spectrometry, in metabolic profiling (Richardson et al., 2008).

6. GLYCOMICS

In its basic form, the glycome can be thought of as the biological equivalent of the proteome and genome. It is challenging to compare the proteome and metabolome to the genome since they are always attached to proteins, which are intimately correlated to the genome. However, proteins assemble together to produce an increasing number of metabolic products. In three important fields of genomics, proteomics, and metabolomics, glycans are connected in a unique way (Joo An *et al*,. 2009).

6.1. Types of Glycans

Studying all the different forms of glycans and their glycoconjugates is highly challenging dueto the wide variety of glycans. Glycoproteins are the most prevalent glycoconjugates in humans. Therefore, glycoproteins were solely bonded by N-linked and O-linked glycans. Glycolipids, peptidoglycans, and glucoseaminoglycans are examples of other glycoconjugates. Glycomics represents a new approach to finding cancer biomarkers (Kronewitter *et al.,* 2009).

7. BIOMARKERS

Biomarkers are quantifiable biomolecules that depict typical physical conditions or shifts in biomolecule aggregation reveal illness states. Changes in proteins or enzymatic processes could be biomarkers. metabolites, or b). These can identify the early signs of sickness (Denorey *et al*., 2013).

7.1. Origin Of Biomarkers

The medical sciences have advanced to the point where it is now possible to define and categorize a physiological phenotype, disease, or biological problem with a high degree of certainty. Researchers, physicians, and medical professionals have been attempting to identify medical anomalies. As early as 26 centuries ago, studies of medical remedies were conducted. After the core dogma of molecular biology, the protein product in relation with Biomarkers notifying us about medical phenomenon, Edwin Smith published a medical book for accumulating knowledge about human physiology diseases and disorders regarding matching remedies. Following the discovery of this nucleic acid and protein-based marker, other markers and tools that can serve as useful determinants of other biological states, illnesses, and medical conditions were also identified (Wilson *et al.,* 2015).

7.2. Types of Biomarkers

As quantitative signs that may indicate a particular biological condition such as a disease or disorder, "biological markers," now commonly known as "biomarkers," are so described. There are

many different kinds of biomarkers, some of which the medical world currently regards as paradigms and some of which (mRNA) are rapidly emerging as significant and potent indicators of biology and illness. The development and structure of all cells, molecules, enzymatic reactions, antibodies, or even small metabolites like amino acids may be considered as these biomarkers (Wilson *et al.*, 2015).

7.3. Examples

Types of biomarkers include cells, genes, gene changes, gene products, enzymes, peptides, antibodies, steroids, hormones, micro RNA, glycans, and exosomes. These evaluate or examine typical biological phenomena such as disease states with pathogenicity, drug toxicity, and medication efficacy (Wilson et al., 2015).

7.4. Micro Robotic Drug Delivery

A hydrogel-based soft micro-robot with magnetic actuators and pH responsiveness was introduced by Li *et al*. (2016) for accurate drug administration. The soft micro-robot, which has eight radial arms and was made of biocompatible substances like PHEMA and PEGDA with Fe3O4 nanoparticles, had extraordinary powers. The hydrogels were characterized by a variety of tests, and the effectiveness of the micro-robot was evaluated. It was examined how the hydrogels responded to pH variations by expanding and contracting. A magnetic field was used to manipulateand release drug-carrying microbeads, and it was seen that the micro-robot's shape changed depending on the pH level. Additionally, PCL-DTX anti-cancer medication microbead cytotoxicity studies yielded encouraging findings, highlighting the promise of this novel soft micro-robot for targeted drug delivery in cancer detection and therapy.

8. OVERVIEW ON EXISTING MARKERS

Circular RNAs (circRNAs) and exosomes have been explored as potential biomarkers for the detection of cancer by Li, Y., et al. (2015). CircRNAs are stable RNA molecules that have been reported to be prevalent in exosomes. They exhibit distinct expression patterns in certain cell typesor throughout development. Exosomes are tiny vesicles that different cell types produce. They carry a cargo of mRNA, microRNA, and proteins that can influence the behavior of receiving cells.

Ren S., et al. (2016) assessed distribution patterns of IgG galactosylation in 12 different cancer types (gastric, liver, lung, ovarian, colorectal, esophageal, pancreatic, renal, prostate, bladder, breast, and cervical cancers) and reported for the first time that the Gal-ratio of IgG (galactosylation pattern of Immunoglobin G (IgG) glycoprotein in serum) has a common feature in multiple cancer types in two different cohorts. These 12 cancer types could be distinguished from non-cancerous controls using IgG Gal-ratio analysis. When IgG Gal-ratio was utilized to separate early-stage tumors from non-cancer controls, similar results were observed. The distribution of IgG galactosylation shows a lot of potential for application as a non-invasive pan-cancer biomarker for early-stage cancer diagnosis and cancer screening, according to all the studies.

Metabolites can be useful biomarkers for the detection and treatment of cancer. Bamji-Stocke, S., *et al*., (2018) reported a number of metabolites that may serve as lung cancer biomarkers. Notably, lactate is connected to the Warburg effect and LDH, indicating its association with aggressive tumor behavior. Lactate is elevated in both lung tissue and serum of lung cancer patients. Increased ATP generation, which is essential for tumor growth, is associated with elevated creatinine levels in tumor tissues. Higher amounts of glutamate, which is produced by glutamine in hypermetabolic tumor cells, are seen in lung tumors and serum samples. On the other hand, lung cancer patients had decreased histidine levels, which could be a diagnostic biomarker. The metabolites can serve as a promising biomarkers for the early detection and treatment of cancer.

It is well known that abnormalities in metabolism cause cancer to develop, but the processes by which these changes cause the malignancy are still poorly understood. Reactive oxygen species (ROS) produced during metabolism lead to changes in gene expression. Aerobic glycolysis is induced by oncogene activation and the loss of tumor suppressors (Warburg effect). In addition to glutamine, glucose is used in glycolysis to create ATP, NADPH, and carbon skeletons for the growthof new cancer cells that survive under oxygen deprivation. (Patal and Ahmad, 2015).

Metabolite markers that serve as bio-signature may shed light on this issue and provide the solution. More than 20 tumor indicators are currently in use, according to the National Cancer Institute, and many gene- and protein-based biomarkers have been utilized successfully for cancer detection (Petal and Ahmad, 2015).

8.1. Role of Biomarkers in Cancer Metabolism

A timely cancer diagnosis can save a person's life. Central carbon metabolism (CCM) and the interactions between glycolysis, the tricarboxylic acid (TCA) cycle, and oxidative phosphorylation are the aspects of cancer metabolism that have received the most attention. The main functions of markers in aiding cancer treatment are in disease diagnosis. The various cancer stages can be identified using markers (Petal and Ahmad, 2015).

9. MODES OF DETECTIONS OF BIOMARKERS IN CANCER TREATMENTS

Global metabolic profiling and related methods for tracking metabolite changes using analytical techniques and assays are the focus of metabolomics. NMR spectroscopy, LC/MS, and GC/MS are methods used in metabolomic profiling for cancer treatment. Using methods created in the domains of statistics and computer science, bioinformatics continues to be a crucial componentof data analysis of gathered data sets (Spratlin, 2009).

10. DISCUSSION

A major global health issue that has a significant influence on mortality and quality of life is cancer. Early cancer identification still presents a serious challenge, despite significant advances in medical knowledge. According to data from the World Health Organization (WHO), 10 million people died from cancer and 18 million new cases were reported globally in 2020, highlighting the need of finding a solution to this complicated problem.

The low 5-year survival rate for some cancer kinds, lung cancer being a notable example with only a 21% survival rate, is one of the most worrisome features of the disease. Nevertheless, recent advancements in precision medicine, utilizing state-of-the-art tools like next-generation sequencing, targeted therapy, and immunotherapy, have markedly improved the therapeutic outcomes in a variety of cancer types.

Due to their unique mechanisms of action and lesser toxicity when compared to conventional cytotoxic chemotherapy, targeted drugs like monoclonal antibodies and small molecule inhibitors have completely changed the way that cancer is treated. The treatment plans for some common diseases, suchas lymphoma, leukemia, multiple myeloma, breast, colorectal, lung, and pancreatic cancers, now include these targeted therapies. There is no disputing their contribution to better patient outcomes.

Cancer is still a powerful enemy despite these medical advances. Traditional cancer treatments frequently fall short of expectations and even harm healthy cells. One of the most difficult aspects of treating cancer continues to be the targeted delivery of medication to tumor cells. Researchers are now focusing on investigating stimuli-responsive hydrogel-based drug delivery systems, which have the ability to regulate drug release from micro-structures and minimize consequences.

Hydrogels, which are highly valued for being biodegradable and biocompatible, are used in biomedicine for a variety of things, including microrobots, drug delivery systems, and more. Their versatility allows them to manage a variety of responsive objects and materials, which could lead to improvements in the treatment of cancer.

Although metabolomics is a new topic in cancer research, it has the potential to provide greater understanding of cancer metabolism. For a long time, studies on cancer metabolism have focused on topics including central carbon metabolism, glycolysis, TCA cycle, oxidative phosphorylation. Otto Warburg postulated the Warburg effect in 1956, which claimed the cancer cells have enhanced glycolytic activity even when oxygen is present. It is commonly agreed that tumors show increased glycolysis associated with decreased TCA cycle and oxidative phosphorylation activity, despite the fact that there is no universal rule for cancer metabolism.

The most recent omics technology, metabolomics, makes it possible to follow and identify metabolic alterations linked to diseases and their reactions to treatments. It offers insightful information about phenotypic changes and molecular physiology, which is very useful for evaluating cancer therapy. By tracking changes in molecular profiles, metabolomics has the potential to improve early cancer diagnosis by identifying metabolic and biomarker changes connected to cancer. Our understanding of how cancer cells use energy for growth and vascularization has improved as a result of the "Warburg Effect," which is characterized by increased aerobic glycolysis in cancer cells.

The discovery of cancer-specific diagnostic biomarkers is the main objective of the majority of metabolomics cancer research. Biomarkers are objectively quantifiable traits that show typical biological processes or responses to therapeutic interventions, according to the Food and Drug Administration (FDA). Diagnostic biomarkers act as proxies for gene, protein, and tumor size, enabling the early identification of particular diseases in patients. While predictive biomarkers evaluate the likelihood that a patient will respond to a particular medicine, prognostic biomarkers estimate sickness risk and forecast patient outcomes.

11.CONCLUSION

The importance of metabolomics in cancer research has been emphasized in this review, which also discusses the potential of metabolites to serve as biomarkers for the early identification and treatment of cancer. The goal of finding novel biomarkers is to enhance cancer diagnosis and patient outcomes. The domains of metabolomics and glycomics, which are in development, provide new opportunities for this purpose. Future studies should continue to investigate these stimulating areas, with a particular emphasis on improving diagnostic precision and comprehending the complex interplay between metabolic profiles and clinical characteristics in cancer patients.

Future disease research will primarily focus on developing a thorough understanding of how metabolic functions are coordinated inside the body and how these understandings can be actually used in clinical settings for objectives such as disease detection, prevention, and therapy. To acquire significant data and reach insightful conclusions, this frequently entails carrying out significant prospective clinical research on a wide scale.

However, there are some significant obstacles to be overcome. The requirement to synchronize and normalize data gathered from multiple sources and trials is a big challenge. It is possible for different datasets to differ in terms of their format, level of quality, and procedures employed to gather them. Researchers must create methodologies and standards to ensure that the data is consistent and can be processed successfully in order to make sense of this plethora of data.

The uniformity of research protocols is another difficulty. For carrying out experiments and gathering data, researchers must create standard operating procedures and guidelines. This guarantees that findings are trustworthy and similar across many investigations.

Adopting a targeted and functional analytical approach is one effective tactic in this area. With this method, diagnostic or prognostic biomarkers are chosen more carefully based on their applicability and utility in the context of particular diseases. The list of biomarkers will be narrowed down to those that are most pertinent and useful for therapeutic applications.

Numerous minor metabolites have already been discovered to offer potential as biomarkers or predictors of disease. To choose the most significant and therapeutically relevant possibilities, further

study is necessary due to the vast amount of these metabolites. This ongoing investigation will contribute to our understanding of the complex mechanisms underlying changes in the internal balance of the body and present promising directions for the advancement of healthcare and customized medicine.

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