

# The significance of metabolic fingerprinting in carcinogenesis

Ayodele Ademola Adelakun<sup>1\*</sup>, Princess Adekunbi Owokalade<sup>2</sup>

<sup>1</sup>Department of Medical Laboratory Science, Ladoke Akintola University of Technology, Ogbomoso 210001, Nigeria. <sup>2</sup>Department of Medical Laboratory Science, Babcock University, Ilishan-Remo 121103, Nigeria.

\*Corresponding to: Ayodele Ademola Adelakun, Department of Medical Laboratory Science, Ladoke Akintola University of Technology, PMB 4000, Ogbomoso 210001, Oyo State, Nigeria. E-mail: adelakunaa@gmail.com.

## Author contributions

Both authors designed the topic. Princess Adekunbi Owokalade carried out the literature search. Princess Adekunbi Owokalade wrote the first manuscript draft, Ayodele Ademola Adelakun reviewed and revised the draft before sending for peer-review. Ayodele Ademola Adelakun handled the correspondence. Both authors approved the final draft.

## Competing interests

The authors declare no conflicts of interest.

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## Abbreviations

ATP, adenosine triphosphate; DNA, deoxyribonucleic acid; ER, estrogen receptor; FASN, fatty acid synthase; GGR, glutamate to glutamine ratio; NADH, reduced nicotinamide adenine dinucleotide; NMR, nuclear magnetic resonance; ROS, reactive oxygen species; TCA, tricarboxylic acid/ citric acid.

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## Abstract

Carcinogenesis describes the process through which normal cells transform into malignant cells (cancer). There were an estimated 18.1 million new cases of cancer (all cancers combined excluding non-melanoma skin cancer) worldwide in 2020: 8.8 million (48%) in females and 9.3 million (52%) in males, giving a male: female ratio of 10:9.5. It may be initiated by the action of biological, physical, or chemical agents that cause a non-lethal, permanent, DNA error on the cell with a consequence of altered cell metabolism. This altered cell metabolism include the Warburg effect, altered lipid and amino acid metabolism and production of various metabolites. It also results in unique metabolic dependencies that, in some cases, can be targeted with precision medicine and nutrition, including drugs that selectively target metabolic enzymes. Metabolic fingerprinting has been applied to the study of carcinogenesis and is particularly helpful in early diagnosis, staging and choice of treatment, thus improving health outcomes. This technology could therefore be harnessed effectively while combining with other omics technologies.

**Keywords:** cancer; metabolomics; prognosis; diagnosis; fingerprint

## Introduction

Carcinogenesis, also known as oncogenesis or tumorigenesis, describes the transformation of normal cells into malignant cells. It is a multi-stage and multi-step process characterized by cellular metabolic changes, genetic and epigenetic changes as well as abnormal cell proliferation [1]. Maintenance of equilibrium between cell division and apoptosis is an homeostatic mechanism that regulates cell populations in tissues and organs. However, DNA mutations and epimutations may disrupt this equilibrium and interfere with the apoptotic process resulting in uncontrolled cell division [2]. This uncontrolled proliferation is accompanied by dysregulated metabolism [3, 4] which results in characteristic metabolic phenotypes that can be explored for early cancer detection, patient selection strategies for clinical trials, and/or as biomarkers of treatment response [5].

Many types of cancer are detected at an advanced stage, subjecting patients to limited treatment options and poor prognosis. Timely cancer detection however improves outcome, allowing more treatment options and better chances of successful intervention, potentially preventing the disease from progressing to an advanced stage [6]. Interestingly, both cancer and cancer therapy modulates a person's metabolic status. These modulations interact intricately with the metabolic benefits of diet and exercise, thus impacting on prognosis and quality of life.

Traditionally, the assessment of metabolic changes has been through the measurement of specific biomarkers using routine laboratory and imaging techniques [5]. Metabolomics, on the other hand, describes the systematic analysis of a wide range of metabolites in blood, urine, tissue extracts, and other bodily fluids. The organs of the body produce or utilize specific metabolites that can serve as metabolomic fingerprints in health and different pathophysiological conditions [7]. Thus, metabolomic fingerprinting provides a unique opportunity for the use of metabolites as a panel of biomarkers of different diseases, including cancer, which can exhibit highly specific metabolic signatures that have both diagnostic and prognostic value.

The objective of metabolomics is to detect and identify endogenous and exogenous metabolites in order to define the genotype or phenotype of a biological system. This might entail the measurement of extracellular metabolites that are secreted and/or excreted from cells into the environment [8]. The metabolome is therefore described as a metabolic “fingerprint” that indicates the state of an organism at a particular time [9].

Metabolic fingerprinting is a commonly used approach towards untargeted metabolomics, aiming to compare the statuses of metabolites that change in response to various stimuli such as disease, environment and toxin exposure [10-12]. This high-throughput analytical technique mostly uses spectroscopic methods for the classification of samples based on their origin or biological relevance [13]. It involves identifying and analyzing unique metabolic profiles associated with the development and progression of cancer. These metabolic fingerprints provide invaluable insights into the underlying metabolic alterations that occur during carcinogenesis and help understand the significance of these changes.

## Metabolic changes in carcinogenesis

Cancer causes metabolic alterations in cancer cells and normal tissues [5]. These alterations interact with intrinsic and extrinsic factors to affect systemic metabolism.

When normal cells proliferate rapidly in response to external growth signals, diverse signaling pathways are activated to suppress oxidative phosphorylation and enhance glycolysis as well as anabolic metabolism to support cell growth. Cancer cells, on the other hand, hijack this process to meet developmental needs even when there are no external signals [14]. In contrast to normal cells in which there is always a negative correlation between glycolysis and oxidative phosphorylation, cancer cells possess these two modes coexisting to disparate degrees [15]. Furthermore, unlike normal cells in which

adenosine triphosphate (ATP) is produced from glucose-derived pyruvate through oxidative phosphorylation via the citric acid cycle (TCA cycle), most cancer cells depend on the less efficient glycolysis in spite of prevailing aerobic conditions [16]. This dual metabolic natures exhibited by tumour cells imply that they could switch back to oxidative phosphorylation phenotype from aerobic glycolysis upon induction of lactic acidosis [17]. Interestingly, a two-compartment tumour metabolism referred to as reverse Warburg effect or metabolic coupling is exhibited by some tumours, indicating that glycolytic metabolism in the cancer-related stroma sustains the adjacent cancer cells.

## Metabolic changes in breast cancer

Breast cancer is the commonest type of malignancy and the second largest cause of cancer-related mortality globally among women [18, 19], while metastatic breast cancer has been reported to be responsible for more than 90% cancer-related deaths [20]. While certain metabolic fingerprints are shared among cancers, breast cancer exhibits some unique metabolic features.

Estrogen and progesterone receptor-dependent metabolism: hormone receptor-positive breast cancers (those expressing estrogen and progesterone receptors) often rely on estrogen for their growth. Estrogen metabolism, including the synthesis and breakdown of estrogen, plays a crucial role in the progression of these subtypes [21].

HER2/neu oncogene-related metabolism: HER2/neu oncogene is a member of the epidermal growth factor receptor family and its amplification is one of the most common genetic alterations associated with human breast cancer. In fact, in vitro and in vivo studies in transgenic mice have shown that HER2/neu is an early event in breast carcinogenesis and enhances metastatic potential [22]. HER2 gene amplification and HER2 protein overexpression have been reported in 10% to 40% of human breast cancers and are shown to induce cell transformation [23]. HER2-positive breast cancers, characterized by overexpression of the HER2/neu protein, exhibit altered signaling pathways that impact metabolism. In breast cancer patients, HER2 overexpression has been linked to tumor aggressiveness, prognosis, and response to hormonal and cytotoxic treatments [24].

Lipid metabolism alterations: breast cancer cells often display distinct alterations in lipid metabolism [25]. Some studies suggest that the metabolism of specific lipid molecules, such as phospholipids and fatty acids, differs in breast cancer compared to other cancer types. To maintain a highly proliferative state, cancer cells either reinforce de novo lipid and cholesterol biosynthesis or activate the uptake of exogenous lipids and lipoproteins thus influencing lipid and cholesterol metabolisms [26]. Also, the expression of fatty acid synthase (FASN), an important enzyme in fatty acid synthesis, is elevated in breast cancer [27]. This underscores the reliance of tumor cells on de novo fatty acid synthesis to satisfy the increased metabolic demand due to rapid growth and proliferation.

Amino acid utilization: breast cancer cells have been found to have specific alterations in amino acid metabolism supporting their growth and proliferation. For instance, Glutamine and its metabolites such as antioxidants Nicotinamide Adenine Dinucleotide (NADH), and glutathione (GSH), participate in energy supply, supplement glucose metabolism and annihilating oxidative stress in favour of proliferation and progression of tumor cells [28]. Notably, a higher glutamate-to-glutamine ratio (GGR) was observed in breast tumor than normal tissues, especially in estrogen receptor (ER) negative tumors. These GGR levels dramatically correlated with ER status and tumor grade [29]. Furthermore, The glutamine metabolism-related proteins, such as GLS-1, glutamate dehydrogenase (GDH), and ASCT2 were found to be highly expressed in HER2-positive breast cancer than other subtypes, which indicated that HER2-positive breast cancer had the highest glutamine metabolism activity [30].

## Metabolic fingerprints in lung cancer

The regulation of metabolic pathways in lung cancer, such as anaplerotic pyruvate carboxylation, has been altered resulting in a more active glycolysis [31]. While studying the metabolic

characteristics of lung cancer in lung tissues from patients, metabolic alterations have been observed as elevated levels of aspartate, phosphocholine, glycerophosphocholine, and lactate, and noticeably decreased levels of glucose and valine [32]. High levels of maltose, glycerol, palmitic acid, glutamic acid, lactic acid, and ethanolamine have also been observed in lung cancer on one hand while decreased levels of amino acids such as lysine, tryptophan, and histidine were observed on the other hand [33]. Increased levels of aldehyde have been detected in the breath of lung cancer patients, which may be connected to 4-HNE, a main consequence of lipid peroxidation [34]. Furthermore, metabolites in serum, plasma and bronchoalveolar lavage fluid (BALF) have also been reported in varying amounts in different subtypes of lung cancer [35-52].

#### Alterations in gastric cancer

Gastric cancer (GC) is the fifth common type of cancer and the fourth-leading cause of cancer-related mortality globally, resulting in approximately 2 million cases of new GC patients and around 0.8 million deaths related to GC per year, according to a recent data from International Agency for Research on Cancer [53].

Three metabolic pathways were upregulated during the investigation of changes in metabolic pathways in gastric cancer cells overexpressing GADD45B [54], a gene implicated in carcinogenesis in chronic atrophic gastritis: the metabolism of fructose and mannose, D-glutamine and D-glutamate, and amino sugar and nucleotide sugar. On the other hand, seven pathways showed downregulation: Glycosylphosphatidylinositol (GPI)-anchor biosynthesis, Neomycin, kanamycin, and gentamicin biosynthesis, N-Glycan biosynthesis, Linoleic acid metabolism, Arginine and proline metabolism, Ether lipid metabolism, and Pantothenate and CoA biosynthesis [55]. In a large scale, multicenter study performed by Xu et al [55], a metabolic panel consisting 21 metabolites was identified in selected features, including formic acid,  $\gamma$ -butyrolactone, alanine, acetic acid, succinic acid, acetoacetic acid, glycolic acid, creatinine, 2-aminoacrylic acid, pyruvic acid, lysine, valine, succinylacetone, 4-acetamidobutanoic acid, glutamine, norcotinine, ornithine, pyridoxamine, urocanic acid, O-phosphothreonine and syringolsulfate. Specifically, 11 of them (formic acid,  $\gamma$ -butyrolactone, acetic acid, succinic acid, glyconic acid, pyruvic acid, lysine, succinylacetone, pyridoxamine, urocanic acid and syringolsulfate) were upregulated, while the other 10 metabolites (alanine, acetoacetic acid, creatinine, 2-aminoacrylic acid, valine, 4-acetamidobutanoic acid, glutamine, norcotinint, ornithine and O-phosphothreonine) were downregulated in gastric cancer group compared with non-gastric cancer group.

#### Applications of metabolic fingerprinting

Metabolic fingerprinting capitalizes on the metabolic signature of cancer to assess disease risk or for prompt detection, diagnosis of specific disease subsets, and monitoring of treatment. It is also important in informing the rational selection of targeted therapies to match the metabolic dependencies of cancer.

#### Understanding tumour heterogeneity

It is widely accepted that tumorigenesis involves sequential accumulation of genetic mutations that ultimately give rise to malignancy. Inflammatory and metabolic factors contribute indirectly to tumorigenesis by generating reactive oxygen species (ROS) and creating an environment permissible to oncogenic mutations and epigenetic alterations. Metabolic fingerprinting identifies unique metabolic profiles associated with diseases, aiding in early diagnosis and the discovery of biomarkers for specific cancers [5].

#### Early detection of cancer

Metabolomics can detect cancer at an early stage, often before conventional diagnostic methods such as imaging or biopsies. It helps identify specific metabolites or patterns of metabolites that are characteristic of different types of cancer. This early detection can lead to more effective treatment and improved survival rates.

Metabolic fingerprinting can also distinguish between various types of cancer and even different stages of the same cancer, aiding in accurate diagnosis and treatment planning. It can detect cancer recurrence earlier than other methods, enabling timely intervention [6].

#### Predictive biomarkers

Techniques for detecting cancer are crucial not just for the first diagnosis but also for screening the right populations, determining the initial course of treatment, gauging its effectiveness, and monitoring cancer progression over time. Two known biomarkers, 5-hydroxymethyl-2-deoxyuridine and 8-hydroxy-2-deoxyguanosine, in breast cancer have been confirmed using the metabolic fingerprint techniques. These cancer markers are highly related to metabolites which are responsible for oxidative DNA damage and DNA methylation process [56]. Although, these biomarkers can be measured using conventional immunoassay techniques, metabolic fingerprinting can be applied for earlier diagnosis banking on its lower detection limit.

#### Monitoring treatment response

Changes in metabolic profiles during cancer treatment can be tracked with their metabolic fingerprint. This allows for the assessment of treatment effectiveness and the adjustment of therapy if necessary. Metabolic fingerprinting can provide early insights into treatment responses. Detecting metabolic changes in response to treatment before clinical symptoms or imaging changes occur can help adjust treatment strategies promptly. It also aids in assessing how the body metabolizes drugs (pharmacokinetics) and how these drugs affect metabolic pathways (pharmacodynamics). This information can guide dose adjustments and optimize treatment regimens. By understanding how a patient's unique metabolism responds to treatment, healthcare providers can select the most effective therapies with minimal side effects [56].

#### Challenges and limitations

##### Ethical issues

The kind of experiment that can be carried out and the population that can be involved may be restricted by ethical considerations. Such ethical challenges may be related to informed consent, privacy, conflict with scientific goals, resource constraints, regulatory compliance stakeholder interests, vulnerable population, and global variations in ethical standards.

##### Sample source

To research or analyze biofluids, which are the combined output of interactions between several organs, one must select the cell or tissue type because each kind of cell and tissue has its own distinct metabolic fingerprint. The most often utilized biofluids in metabolomics are plasma and urine because they are relatively simple to obtain and can be collected with no or minimal invasion, allowing for high-frequency sampling even in critically ill patients. They constantly maintain a dynamic equilibrium with the body and quickly reflect alterations in host metabolism. It should however be noted that urine offers a time-averaged depiction of the condition of an organism, whereas plasma reflects a snapshot of that state. Cerebrospinal fluid, saliva, semen, and different tissue samples are less frequently used as study samples. The origins of metabolites can be studied using tissue samples because, unlike biofluids, they can be utilized to quantify organ-specific metabolic signatures [9].

##### Data analysis methods and software

One of the main challenges in metabolomics is that the large volume of data produced requires the use of complex multivariate analysis techniques. Although none of the currently available data collection methods can capture the quantitative and qualitative information on all metabolites in a given sample, all methods still generate and process immense amounts of information. For example, data collected by 1H NMR spectroscopy contains information on up to 100

metabolites in urine and up to 30 in plasma and tissue extracts, whereas data collected by MS-coupled techniques can contain information on more than 1000 metabolites per sample. Extracting meaningful data for biological interpretation from this vast amount of data requires the use of robust computational techniques [9].

### Biological variation

Finding generally applicable metabolites that are suggestive of disease might be challenging due to biological heterogeneity in metabolic fingerprint. In addition to these factors, metabolites differ with circadian rhythms, diet, age, sex, and weight, which can be challenging to regulate, particularly in human studies where there are several ethical and practical restrictions [5].

### Insensitivity of most common data generation methods

Due to its affordability and high productivity, <sup>1</sup>H-NMR spectroscopy is the most widely used technique, however it cannot detect metabolites at low concentrations. Since many of the high-concentration metabolites tested are present in numerous pathways, they are not particular to any one response. Despite the fact that these high-concentration metabolites can change significantly during a perturbation, their ubiquity reduces their usefulness as reliable biomarkers because it can be challenging to identify precisely which pathways are affected [5].

### Standardization and reproducibility

Lack of standardization in sample collection, preparation, and analysis can lead to variability between studies. Metabolite levels are highly dynamic and can change rapidly, making it challenging to capture the full metabolic profile at a single time point [9].

### Complex data

The huge amount of complicated data generated by metabolomics necessitates multivariate analytic methods [9].

### Future directions

#### Personalized healthcare

Although metabolic fingerprints have just lately begun to have a major impact on pharmaceutical and biological research, they are quickly spreading throughout the field and provide a vital edge in illness diagnoses. It will play a significant role in pharmacology in the future and will help to enable personalized healthcare. It can be used in drug development (*in silico* models can be created to predict the effects of drugs on metabolic phenotypes before *in vivo* testing). Treatment approaches could be more successful if metabolic prescreening was utilized to forecast how an intervention would turn out [9].

#### Integration with genomic and proteomic data

The integration of genomes, proteomics, and metabolomics will be the biggest contribution of metabolic fingerprinting since it will advance our basic biological knowledge and have an effect on numerous fields of biomedical study. To properly predict illness development and pharmacological intervention, the results at each level can be clearly measured and integrated, as opposed to assuming or attempting to quantify unknown information. Understanding alterations in protein concentrations and gene expression at the cellular and whole-organism levels will aid in determining the biological roles of these entities. At the phenotypic level, interactions between the environment and the organism can be examined and may provide insight into epigenetic therapies or chromosomal alterations [57].

### Diagnostics

Metabolomics has the potential to significantly enhance illness diagnoses because it generates enormous amounts of data using relatively inexpensive and noninvasive approaches. In the end, metabolomics applied to clinically usable urine or blood samples can be used for diagnosis in a variety of situations, including in patients

who are critically ill. Recent developments in microfluidics provide a promising technological advancement in that area for a more extensive use of metabolomics profiling [58].

### Targeted therapies based on metabolic profiles

Numerous cancer types, including leukemia, lymphoma, nasopharyngeal cancer, breast cancer, colorectal cancer, and bronchogenic carcinoma, have been studied using metabolomics [59]. The use of metabolic fingerprinting to guide cancer patient care has also showed potential. For instance, there is a correlation between certain metabolite levels in urine before chemotherapy and weight gain (or lack thereof); hence, this information could be used to identify people who need treatment.

### Conclusion

It is widely acknowledged that one of the characteristics of cancer is a modification in cell metabolism, which has been described as carcinogenesis. Metabolomics has made tremendous progress in influencing key aspects of oncology, such as screening, diagnosis, and treatment. It has enormous potential for use in the advancement of biomedical and healthcare sciences. Drug development, disease diagnosis, personalization of healthcare, and noninvasive drug toxicity detection has all benefited from and will continue to benefit from metabolic fingerprinting. Due of its current lack of sensitivity, metabolomics may not have an immediate role in all areas, although this will change as researchers continue to develop methods to improve sensitivity. Finally, instead of the single metabolic fingerprinting analysis, the integration of multi-omics datasets (such as metabolomics, proteomics, and genomics) would be beneficial to interpret the complex biological systems for clinical application and with that understanding, much more could be learned about the biology of complex biological system.

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