REVIEW ARTICLE

Metabolomics in precision medicine: Application and prospect in cancer research

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Abstract

Metabolomics is the most recent and final discipline among the post-genomic, multiomics fields. It encompasses key technologies in systems biology, providing an overview of low-molecular-weight metabolites while examining disturbances to offer pathophysiological explanations. The two key analytical tools in metabolomics are nuclear magnetic resonance spectroscopy and mass spectrometry, which includes gas chromatography-mass spectrometry and liquid chromatography-mass spectrometry. Metabolomic research relies on a three-stage data generation process: the first stage involves precise analytical chemistry to produce data; the second stage employs multivariate statistical analysis; and the last stage uses big data as a reference for comparison to establish biochemical, metabolic, and pathophysiological correlations, thereby providing possible interpretations. The initiative of precision medicine starts with cancer as the first disease target. This review discusses and illustrates the application of metabolomics in precision medicine, choosing two types of cancer as example. Warburg effect and metabolic reprogramming are particularly discussed. By providing global, top-down, and less biased information, metabolomics enables precision medicine.

Keywords: Lung cancer, Metabolic reprogramming, Precision medicine, Prostate cancer, Warburg effect

1. Introduction

Metabolomics is the most recent and final discipline among the post-genomic multiomics fields [1,2]. It encompasses key technologies in systems biology, providing a global, top-down, and unbiased view of low-molecular-weight (LMW) metabolites while examining meaningful disturbances to offer pathophysiological explanations. The two key analytical tools in metabolomics are nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS), which includes gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-mass spectrometry (LC-MS) [3–6]. Metabolomics has been applied in many fields of life science and most extensively in precision medicine [7,8]. The first disease type is cancer [9,10] and the second disease type is diabetes [11,12].

Metabolomic research relies on a three-stage data generation process: the first stage involves precise analytical chemistry to produce data; the second stage employs multivariate statistical analysis; and the last stage uses big data as a reference for comparison to establish biochemical, metabolic, physiological, and pathological correlations, thereby providing possible underlying interpretations (Fig. 1).

This review aims to introduce metabolomics in multiomics and illustrates the application of metabolomics in precision medicine, emphasizing its potential and prospects in cancer research. It is not an additional review with extensive literature survey or a meta-analysis containing data from clinical trials of anticancer drugs. A summary of definitions of metabolomics is shown in Table 1.

In conclusion, metabolomics is an emerging field of multiomics, which aims to provide researchers

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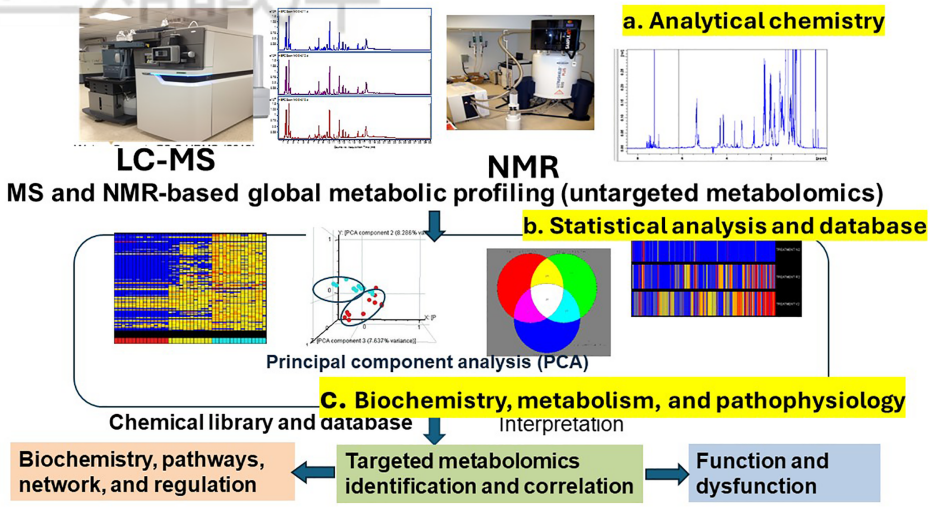

Fig. 1. Three layers of knowledge for metabolomic studies. Metabolomic research relies on a three-stage data generation process: the first stage involves precise analytical chemistry to produce data; the second stage employs multivariate statistical analysis; and the last stage uses big data as a reference for comparison to establish biochemical, metabolic, physiological, and pathological correlations, thereby providing possible underlying interpretations.

with novel analytical tools to better understand the metabolic components and networks within the cell and other biospecimens, commonly referred to as the metabolome, chemical individuality, molecular fingerprinting, or phenome (by Nicholson et al.) [1]. By comparing human genome of about 22,000 genes and proteome of about 100,000 protein species, human metabolome contains approximately 12,00 LMW (MW < 1600 Da) metabolites.

2. Key approaches in metabolomic studies: untargeted and targeted metabolomics

2.1. Untargeted metabolomics

There are two major approaches in metabolic studies, untargeted (or non-targeted) metabolomics and targeted metabolomics. Without knowing the metabolite identity or concentration in the beginning, untargeted approach aims to search for potential metabolites, which may contribute for differentiating the multivariate study group into sub-groups. Namely, it is an approach to find if the differential metabolites, in identities and/or in concentrations between sub-groups, are greater than those within the original groups. Untargeted metabolomic approach is a hypothesis-generating approach. For example, among a diversified group of type 2 diabetic patients, potential metabolites may exist (plasma glucose, triacylglycerols (TG), or branched-chain amino acids (BCAAs; valine, leucine, and isoleucine) which may emerge as potential metabolites to re-grouping the entire diabetes patients into sub-groups [11,12] (sub-groups as prediabetes, diabetic nephropathy, and diabetic atherosclerosis). Untargeted metabolomics is more difficult to conduct, since global metabolite profiling is needed, indicating reproducibility in analytical chemistry is critical. Large chemical databases (chemical libraries) are also essential. Nowadays, ultra-performance liquid chromatography (UPLC) coupled with Time-of-Flight (TOF) mass spectrometry (UPLC-TOF MS) is applied to achieve this goal. Untargeted metabolomics is costly, time-consuming, and more difficult in data interpretation. However, this approach can shed light on the research direction and can provide a global, top-down, and less biased view of the research topic. Its advantage cannot be achieved by other approaches.

2.2. Targeted metabolomics

Based on the untargeted metabolomic findings with plausible explanations, targeted metabolomics investigates the chemical identities and concentrations of these potential metabolites (as unknown or by using a chemical library). Future studies can establish their biochemistry, metabolism, regulation, crosstalk in metabolic functions, and contribution in the pathophysiology (phenotyping). The above-mentioned approaches are called targeted metabolomics. After validation, these differential metabolites may serve as biomarkers in clinical studies or as biomarkers in drug screening [4]. Biomarkers obtained by targeted metabolomic

Table 1. Definitions of metabolomics (metabonomics) provided by pioneers and scientific organizations.

1. **Metabonomics (Nicholson et al.):** The quantitative measurement of the dynamic multiparametric metabolic response of living systems to pathophysiological stimuli or genetic modification [1]. Metabonomics indicates understanding the metabolic responses of living systems to pathophysiological stimuli via multivariate statistical analysis of biological NMR spectroscopic data (nowadays, NMR and MS) [3–6].
2. **Metabolomics (Fiehn):** A comprehensive and quantitative analysis of all metabolites in a system [2].
3. **The Metabolomics Society (**metabolomicssociety.org): Metabolomics is the comprehensive study of metabolome, the repertoire of biochemicals (small biomolecules) present in cells, tissues, and body fluids. The study of metabolism at the global or -omics level is a rapidly growing field that has the potential to have a profound impact upon medical practice. At the center of metabolomics, there is the concept that a person's metabolic state provides a close representation of that individual's overall health status.
4. **The Metabolomics Society (from the website with minor modifications):** Metabolomics is a newly emerging field of "omics" research concerned with the comprehensive characterization of the small molecule metabolites in biological systems. It provides an overview of the metabolic status and global biochemical events associated with a cellular or biological system. An increasing focus in metabolomics research is now evident in academia, industry, and government, with more than 500 papers a year (Key word search on metabolomics with filters applied in the last 5 years, 64,056 results cited in PubMed on September 15, 2025) published on this subject. Metabolomics is now part of the vision of the NIH road map initiative [8]. Many other government bodies are also supporting metabolomics activities internationally. Studying metabolome will highlight changes in networks and pathways and provide insights into physiological and pathological states. The concept of systems biology and the prospect of integrating transcriptomics, proteomics, and metabolomics data is exciting and the integration of these fields continues to evolve at a rapid pace. Developments in informatics, flux analysis and biochemical modeling are adding new dimensions to the field of metabolomics. To be able to walk from genetic or environmental perturbations to a phenotype and to a specific biochemical event is exciting. Metabolomics has the promise to enable detection of disease states and their progression, monitor response to therapy, stratify patients based on biochemical profiles, and highlight targets for drug design. The metabolomics field builds on a wealth of biochemical information that has been established over years.
5. **The Common Fund's Metabolomics program (US NIH).** The statement is lengthy. However, metabolomics as the last omics deserves a precise description, with scope and prospects, and therefore is quoted with minor revision.

a. **Introduction** Metabolomics is the scientific study of the chemical reactions that occur in organisms, cells, or tissues. Each reaction produces small chemicals called metabolites, which play critical roles in keeping cells healthy and functioning properly. Cells break food into metabolites, such as sugars, amino acids, or lipids, and use these metabolites for energy to power of whole body. These same metabolites can also be used to build new cellular structures and machinery. Cells can also break down other materials into metabolites, sometimes even parts of the cell itself, which can be used to communicate with neighboring cells and send messages all throughout the body. The sum of all the metabolites in the bodies is referred to as metabolome.

b. **Application of metabolomics in human health and diseases.** Whole-body metabolism is impacted by a variety of distinct factors, such as diet, genetic history, the environment, and daily activity. The Metabolomics Program (US NIH) aims to increase our understanding of how such factors can change a person's metabolome. In addition to increasing our understanding of how cells work, metabolomics plays a significant role in understanding of how diseases such as cancer, Alzheimer's disease (AD), and diabetes can affect whole-body health. Since every chemical reaction leaves a chemical fingerprint of the metabolites produced, researchers can use this information to find key changes that occur in disease states. This information can then be used to help develop treatments.

c. **The great impact in promoting human health (on why metabolomics is specifically supported).** Metabolomics is a powerful and emerging field that allows scientists to track the unique fingerprints of chemical reactions in our bodies. Every chemical reaction produces different metabolites, and researchers can use this information to track human health. However, the study of metabolomics has remained a specialized field thus far. The Common Fund's Metabolomics program aims to expand the capacity of researchers to study metabolomics, which is expected to catalyze this important research area and accelerate progress towards harnessing the power of metabolomics to improve human health.

d. **More detailed description.** Metabolomics is the scientific study of the chemical reactions that occur in organisms, cells, or tissues. Each reaction produces small chemicals called metabolites, which play critical roles in keeping our cells healthy and functioning properly. For example, our cells break down the food we eat into metabolites, such as sugars, amino acids, or fats, and use these metabolites for energy to power our bodies. These same metabolites derived from food can also be used to build new cellular structures and machinery. Cells can also break down other materials into metabolites, sometimes even parts of the cell itself, which can be used to communicate with neighboring cells and send messages all throughout the body. The sum of the metabolites in a living system is referred as metabolome.

e. **Application of metabolomics.** Whole-body metabolism is impacted by a variety of factors, such as diet, genetic history, the environment, and daily activity. The Metabolomics program aims to increase our understanding of how such factors can change a person's metabolome. In addition to increasing our understanding of how cells work, metabolomics plays a significant role in our understanding of how diseases such as cancer, AD, and diabetes can affect whole bodies. Since every chemical reaction leaves a chemical fingerprint of the metabolites produced, researchers can use this information to find key changes that occur in disease states. This information can be used to help develop treatments.

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approach are not just one or two metabolites. Targeted metabolomics can generate a portfolio of biomarkers, which are more suitable for monitoring complicated disease progression.

3. Analytical chemistry and multivariate statistical analysis in metabolomic study

Metabolomic study relies on chemical analysis of LMW metabolites in biospecimens including cells, tissues, blood samples (serum, plasma, and whole blood cells), saliva, sweat, feces and others [5]. A summary of the advantages and disadvantages of using NMR and MS as analytical tools is shown in Table 2. Precautions on sample collection and storage conditions are required. LMW metabolites are mostly stable at an ambient temperature. However, protein binding, metabolite leakage from a frozen sample, low recovery from cells (such as RBC) and tissues (surgical removal of tumor tissues) should be considered if quantitative analysis in targeted metabolomics is essential. Any targeted metabolomic study requires quantitation, superior quality control, and validation.

Both GC- and LC-mass spectrometry and NMR spectroscopy provide data beyond simple alpha-numerical figures. For example, GC- and LC-MS provide datasets as retention time, *m*/*z*, and signal intensity. NMR spectroscopy generates chemical shift (δ), coupling constant (J), and signal intensity (I). A core metabolomic laboratory should equip with NMR and MS as two arms of analytical tools. A chemical library is also helpful.

In statistical analysis for metabolomic studies, the most frequently used technique is Principal Components Analysis (PCA), an unsupervised approach

Table 2. Advantages and disadvantages of nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS) as analytical tools in metabolomic study (modified from Wishart [4]).

NMR: Advantages

a. NMR spectroscopy is a reliable and mature technology.
b. Non-destructive quantitation of low-molecular-weight (LMW) metabolites.
c. Rich in information (chemical shift, coupling, and signal intensity).
d. Rapid measurement (within 10 min for each sample) and can be automated.
e. Requires minimal pre-treatment, no separation, or derivatization.
f. Structural and stoichiometric information allows identification of metabolites.
g. Solution NMR can link to metabolite imaging (such as fMRI and MRS).
h. Most spectral features of LMW metabolites are available in literature or databases.
i. Long lifespan for instrument (>20 yr).

NMR: Disadvantages and limitations

a. Low sensitive, only high concentration metabolites can be determined.
b. High cost in instruments and maintenance.
c. ^{1}H-NMR cannot detect non-hydrogen containing metabolites or inorganic ions.
d. As to LC-MS, NMR measurement requires larger sample volumes (0.1–0.5 mL).

LC-MS: Advantages

a. Outstanding sensitivity in detecting most organic metabolites and several inorganic molecules.
b. Small sample volume is needed (1–10 μL).
c. Rich in information for metabolite chemical identity (retention time, m/z, fragmentation pattern in TQ MS, and intensity).
d. It has the potential to detect the largest portion of metabolome. Most suitable for global metabolite profiling (untargeted metabolomics).
e. Mild ionization method (electrospray ionization; ESI) is used.
f. Very flexible technology. Analysis can be done without separation.
g. Metabolite imaging (MALDI or DESI) is possible.

LC-MS: Disadvantages and limitations

a. Mass spectrometry is a destructive analysis.
b. Global metabolite profiling and individual metabolite quantitation are hard to achieve simultaneously.
c. Usually requires separation in a longer separation time (10–30 min for each sample in untargeted metabolomics).
d. Poor resolution and lower reproducibility.
e. Potential metabolite identification is difficult. A sizable portion of spectral features are not yet identifiable, particularly in gut microbiota and plant science.
f. Costly and short instrument lifetime.

to finding a small set of variables that explain the original data set. As those known as supervised methods, statistical models are developed from a training set of multi-parametric dataset, in which multivariate biological samples can be classified into sub-groups (for example, by disease state). A widely used supervised method is Partial Least Squares (PLS) analysis. It can further combine with discriminant analysis methods, which aim to find a linear combination of features that is used purposely to classify data into subsets. Combination of PLS with Discriminant Analysis (called PLS-DA) defines a surface that can be placed in a multi-dimensional plot to separate data into classes [1].

Many software packages are available nowadays. In public domain, a package called MetaboAnalyst (version 6.0) is commonly used. There are two metabolite databases which are open for public use, namely Human Metabolomic Database (HMDB) and Kyoto Encyclopedia of Genes and Genomes (KEGG) for metabolite identification, metabolic pathway mapping, and potential interpretations in pathophysiological states.

4. What can metabolomics do in biomedical science?

Metabolomics, alone or couples with other omics. greatly promotes biomedical research. It is the key platform technology in systems biology [13], in phenotyping, and in providing a global, top-down, and less-biased view of any living system with inherited complexity. Potential biomarkers for specific disease targets can be generated. For example, a follow-up type Framingham study using stored blood samples for predicting diabetes, five amino acids (three branched-chain amino acids, namely valine, leucine, and isoleucine and two aromatic amino acids, name phenylalanine, and tyrosine) predict diabetes, which is better than glucose or HbA1c [12]. A summary of potential research directions by incorporating metabolomics as a key platform is shown in Table 3.

For example, epidemiological studies, which are usually association studies and will not be able to provide the underlying molecular level explanation. Coupling metabolomic design in epidemiological study is known as metabolomic epidemiology) [22]. The findings can be causal in relationship to the risk factors under study.

5. Precision medicine

The announcement by US president Obama on precision medicine initiative aims to bring individuals closer to curing diseases, such as cancer and diabetes, and to provide access to the personalized information to keep individual and their families healthier [7]. For early prevention and better individualized treatment strategies, the prospect of applying this concept has greatly based on the development of a. large-scale biologic databases, such as the human genome sequence (and cancer genomics), b. powerful methods for characterizing patients, such as proteomics, metabolomics, genomics, diverse cellular assays, and mobile health technology, and c. computational tools for large sets of data. The integration of these three approaches makes precision medicine possible.

Genomic studies (GWAS and WGS) have identified risk loci for complex diseases, but effect sizes are typically small and information on the underlying biological processes is often lacking. Associations with metabolic traits as functional intermediates, metabolomics can overcome these problems and inform individualized therapy. A better approach: genotype-dependent metabolic phenotypes using a GWAS/WGS and untargeted metabolomics.

Table 3. What can metabolomics do in precision medicine and in other biomedical research?

1. To diagnose diseases or to predict the interactions of multiple risk factors in disease progression (cancer [4,7,13], diabetes [8–10], and CVD [14–17]). Metabolomics is powerful in monitoring disease landscape.
2. a. To determine whether a therapeutic treatment is effective (pharmaco-metabolomics). b. To target specific patient groups most likely to benefit from a drug treatment (for example, statin treatment in CVD). c. To speed new drug development and to make safer drugs [4].
3. Studies linking phenotyping to genotyping and vice versa.
4. Epigenomics: environmental risk factors, and exposure monitoring [22].
5. Gut microbiota and microbiome [18,19].
6. Precision nutrition, dietary intervention, food science, and toxicology [20,21].
7. Metabolomic epidemiology (from observational to causal) [22].
8. Aging and healthy aging studies: To monitor healthy people from early signs to the advanced stage of a disease [23,24] and treatment outcome, such as heart failure [16].
9. Linking multiomics, particularly between genomics and metabolomics

6. Metabolomics enables precision medicine

Metabolomics at the global level is a rapidly growing field, which has the potential to play a profound impact upon medical practice. At the center of metabolomics, there is the concept that a person's metabolic state provides a close representation of that individual's overall health status. It is anticipated that the narrow range of biochemical

analyses in current use by the medical community today will be replaced soon by analyses that reveal a more comprehensive metabolic signature (metabolomics). In another word, metabolomics enables precision medicine (a statement cited by the Metabolomics Society) [9].

The metabolic signature is anticipated to describe the overall biochemical and metabolic aberrations that reflect patterns of variance in while-body wellness and aid in differential diagnosis and treatment strategies. Sophisticated metabolomic platforms and informatics tools have developed that make it possible to measure thousands of metabolites in cells, blood and other biofluids, and tissues. Metabolomic approaches also enable robust analysis of response to treatment, including targeted therapy and immunotherapy for cancer. New insights have provided underlying mechanisms of major human diseases, namely cancers, diabetes, cardiovascular disease (CVD) [13–15], neurodegenerative diseases (Alzheimer's disease and Parkinson disease) and neuropsychiatric disorders. From information to knowledge, metabolomics has provided a broad spectrum of pathophysiological conditions. In summary, the ultimate goals of precision medicine can be achieved as shown below.

a. Providing predictive, preventive, diagnostic, prognostic, and surrogate markers of diverse disease states on the underlying molecular mechanisms.
b. Allowing for sub-classification of diseases, and stratification of individualized patient care based on the multiomic disturbances impacted.
c. Using multiomics-based (particularly genomics and metabolomics), portfolio of biomarkers for treatment, such as drug response phenotypes, can provide an effective means to predict variations in a patient's response to treatment (tailored therapy and pharmacometabolomics).

In conclusion, precision medicine approach using systems biology (genomics, proteomics, and metabolomics), as compared to treatment failure-based medicine approach in traditional clinical practice, will revolutionize modern medicine practice [9].

7. Cancer as the first disease target in precision medicine

The precision medicine initiative in the year 2015 has pointed out two main components [7]: a near-term focus on cancers and a longer-term aim to generate further knowledge applicable to the full range of human health and diseases. Both components are within reach because of advances in modern research, including molecular cell biology, multiomics, bioinformatics, and artificial intelligence. It is anticipated that the following disease targets in sequence will enter the treatment pipeline of precision medicine, cancer, diabetes, and geriatric medicine. Since targeted therapy is not always available on time, precision nutrition may come to help as an adjuvant therapy or a combination therapy [18,19].

8. Cancer initiation and progression: cancer landscape

Cancer is chosen as the first disease target in the practice of precision medicine. Not just as the most life-threating disease to people, the choice is based on advances in human genome and cancer genomes, which form a large oncology database. Besides genetic aberration, genomic and epigenomic risk factors working together may drive cancer cells to re-program their metabolism, which is called cancer metabolic reprogramming, to achieve growth promotion, survival, proliferation, long-term maintenance, metastasis, and recurrence. The impacts of metabolomics in cancer research are significant and deserve the greatest attention, as illustrated in this review.

A closer look at the types of cancers, which are positively associated with type 2 diabetes, indicates that they are solid tumors of digestive system, metabolism, endocrine organs, and are sex-dependent (breast, endometrium, ovary, and prostate cancers) (Table 4) [25]. A second impression is that their Hazard ratios (HR) in diabetes prevalence, as compared with non-diabetic control, are significant and span in a narrow range. It suggests that the underlying mechanisms of type 2 diabetes in driving cancer prevalence may be similar. Since cancer patients are adults of middle aged to aged population, the disturbances may also link with aging.

Warburg effect in cancer biology deserves great attention. Type 2 diabetes provides a common soil for cardiometabolic diseases and may also promote the progression of several types of cancer. In this review, we choose two cancer types, prostate cancer in male and breast cancer in female, as examples to illustrate the application of metabolomics in cancer research.

9. Warburg effect and cancer development

Warburg effect in cancer biology, the common feature of altered metabolism, is mentioned as an

Table 4. A. Types of cancers which are positively associated with type 2 diabetes and B. types of cancers which type 2 diabetes is not significantly associated with cancer mortality.

A. Types of cancers which are positively associated with type 2 diabetes. Three types of cancer (italic) will be further discussed.

a. Colorectum (HR 1.41; 95% CI 1.26, 1.57)
b. Liver (HR 2.05; 95% CI 1.77, 2.38)
c. Bile duct (HR 1.41; 95% CI 1.04, 1.92)
d. Gallbladder (HR 1.33; 95% CI 1.10, 1.61)
e. Pancreas (HR 1.53; 95% CI 1.32, 1.77)
f. *Breast (HR 1.72; 95% CI 1.34, 2.19)*
g. *Endometrium (HR 2.73; 95% CI 1.53, 4.85)*
h. Ovary (HR 1.60; 95% CI 1.06, 2.42)
i. *Prostate (HR 1.41; 95% CI 1.09,1.82)*
j. Kidney (HR 1.84; 95% CI 1.28, 2.64)
k. Thyroid (HR 1.99; 95% CI 1.03, 3.86)
l. Lymphoma (HR 1.39; 95% CI 1.04, 1.86)

B. Types of cancers which type 2 diabetes is not significantly associated with cancer mortality.

a. Leukemia
b. Bladder
c. Cervix
d. Oesophagus
e. Stomach
f. Lung

increase in glucose uptake accompanied by an elevated production of lactate. Since Warburg effect is commonly observed in solid tumors, it is worthwhile studying its molecular mechanisms using metabolomics. A very readable review summarizes the functions of Warburg effect is as follows [26,27]. Metabolomics has been applied recently in the studies of Warburg effect in cancer metabolic reprogramming. This review summarizes the major observations and plausible explanations as shown below.

9.1. Rapid, but not optimal, ATP synthesis and generation of reducing power

Adapted metabolic reprogramming, in favor of cancer growth, is observed in cancer progression. Adaptation of this type of energy metabolism, which drives more rapidly ATP synthesis and provides reducing power (NADPH), can support the demand for biomolecular synthesis in cancer cells.

9.2. Synthesis of biomolecules for rapidly growing cancer cells

Warburg effect-driven glycolysis and TCA cycle may turn into a status of providing precursors for biosynthesis of proteins, lipids (cholesterol and phospholipids for membrane), and DNA and RNA in favor of cancer cell survival and proliferation. In general, the increased glucose consumption is used as carbon source for anabolic processes in support of cancer cell proliferation.

9.3. Altered tumor microenvironment may lower immune surveillance

Elevated glucose metabolism decreases the pH in the microenvironment due to lactate secretion. A reasonable explanation of Warburg effect outcome is that elevated lactate may contribute to lower pH in cancer microenvironment. The potential benefits of acidity to cancer cells are obvious. The acid-mediated invasion hypothesis suggests that proton ions diffuse into cancer cells and environmental proximity, allowing for enhanced invasiveness and reduced immune surveillance.

9.4. Warburg effect confers direct and indirect signaling functions to support tumor cells

The causal role of altered glucose metabolism and following metabolic reprogramming can promote tumorigenesis. The resulting signal transduction underlying Warburg effect may affect the cellular processes in favor of cancer cell survival, progression, and invasiveness.

9.5. Development of Warburg effect-based biomarkers

A portfolio of biomarkers can be developed to monitor plasma glucose, lactate, alanine, and TCA cycle intermediates in affecting cancer initiation, progression, and drug treatment outcome. The cancer types, which are type 2 diabetes-associated, are most appropriate to follow by this approach. It is anticipated that the biomarkers can be feasible in early tumorigenesis and tumor recurrence. The treatment outcome by targeted therapy and immunotherapy in diabetes-associated cancer types deserve a closer look at their Warburg effect. It is worthwhile developing biomarkers based on Warburg effect and TCA cycle intermediates.

9.6. Prostate and breast cancers as examples

It is timely for this review to discuss the advances in cancer research using metabolomics as a key platform. We chose to introduce a study on prostate cancer in early metabolomics era, entitled metabolomic profiles delineate potential role for sarcosine in prostate cancer progression [28,29].

Aiming to elucidate metabolomic aberrations characterizing prostate cancer progression, LC- and GC-based mass spectrometry are used to profile 1126 metabolites across 262 clinical samples (42 tissues and 110 each of urine and plasma). Untargeted metabolomic profiles are taken to determine benign prostate, localized, and metastatic prostate cancers. Since protein breakdown and metabolite methylation routes were both elevated, sarcosine (N-methyl glycine) is identified as a differential metabolite, which increases during prostate cancer progression to metastasis. Sarcosine levels also increased in invasive prostate cancer cell lines. Knockdown the sarcosine-generating enzyme (glycine-N-methyl transferase) attenuated prostate cancer invasion. Addition of exogenous sarcosine or knockdown of the enzyme that leads to sarcosine degradation (sarcosine dehydrogenase) induced an invasive phenotype in benign prostate epithelial cells. Androgen receptor and the ERG gene fusion product coordinately regulated components of the sarcosine pathway. This study suggests sarcosine as a potential biomarker of prostate cancer cell invasion and aggressivity [28].

Sarcosine is an activator of mTOR signaling pathway. Elevation of sarcosine, caused by mutant glycine *N*-methyl transferase, is observed in metastatic prostate cancer. Sarcosine can be an important metabolic intermediary of prostate cancer cell invasion and aggressivity. Therefore, sarcosine is proposed as a marker of prostate cancer severity and metastasis, based on indication as increase in protein breakdown and elevation in metabolite methylation. Epigenetically implicated, disturbance in DNA methylation has been frequently reported cancer. Sarcosine, betaine, choline, trimethylamine N-oxide (TMAO) are potential markers in response to the disturbances in metabolite-level methylation pathway, starting from the serine glycine route of methylation by S-adenosylmethionine (SAM). Sarcosine is the first methylation product of this pathway (Glycine → Sarcosine → Betaine → Choline → TMA → TMAO).

Sarcosine, choline, and lactic acid are oncometabolites [4]. An oncometabolite is defined as a metabolite with its elevation in concentration may promote cancer growth. A list of oncometabolites is shown: 2-hydroxy glutarate/fumarate/succinate/sarcosine (N-methyl glycine)/glucose/glutamine (Gln/Glu/α-ketoglutarate)/asparagine/choline/lactate [4]. They are metabolites related to Warburg effect and TCA cycle intermediates in response to metabolic reprogramming due to disturbances in carbohydrates, lipids, and proteins. Disturbances in metabolite level are observed in response to environmental risk factors in disease progression, including cancer and cardiometabolic disease.

Linking metabolomics as the key platform technology, a review has reported on the advances and perspectives in prostate cancer biomarker discovery in 5 years (publications before 2021) through tissue and urine metabolomics (Table 5) [29]. The review also aims to identify novel biomarkers for more accuracy to distinguish between indolent to aggressive prostate cancer. A comparison of these two publications on prostate cancer progression and severity is worthwhile [28,29].

A collection of 18 metabolites consistently altered in prostate cancer tissue among different studies includes alanine, arginine, uracil, glutamate, fumarate, and citrate. Urine metabolomic studies also indicate the dysregulation of 15 metabolites and alterations in the levels of valine, taurine, leucine, and citrate between urine and tissue studies. The correlations of metabolomic profiles in tumor-bearing tissues (surgical removal) and biofluids (serum, plasma, saliva, and urine) can differentiate cancer stages and severity.

Warburg effect plays a significant role in cancer biology, particularly in the stages of cancer initiation and recurrence. Insulin resistance, obesity, energy metabolism, and metabolic reprogramming should be considered from a global, top-down, and less-biased point of view. Beyond Warburg effect and metabolic reprogramming, disturbances causing by other risk factors also deserve attention,

Table 5. Differential metabolites identified in metabolomic studies referred to the similar variations in prostate cancer tissues (a review based on the publications for 5 years).

Tyrosine
Succinate
Spermine
Proline
Phosphocholine
N-Acetylglucosamine 6-P
N-Acetylglucosame
Myo-Inositol
Malate
Lactate
Monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs)
Choline
Arginine
Alanine
Uracil
Glutamine
Fumarate
Citrate

Note: Warburg effect and TCA cycle metabolites are marked in **bold phase** [4].

which are inflammation, epigenomic risk factors, immunometabolism, gut microbiota [18,19], lifestyle, sex disparity, and aging. This review does not cover these aspects.

Breast cancer has become the most common cancer in female worldwide. As disease biomarkers, neither CA 15-3 nor CEA provides satisfactory sensitivity or specificity for early diagnosis. Digital mammography and digital breast tomosynthesis are regarded as an effective way to reduce the mortality of breast cancer in age-appropriate asymptomatic women. Genetic advances enable breast cancer diagnosis, which also precisely guides the therapeutic treatment. Nowadays, breast cancer is managed from precision medicine point of view.

It is timely for this review to discuss the metabolomic findings of breast cancer, which is affected by Warburg effect, with those of prostate cancer. A review on 35 MS-based and 6 NMR-based metabolomics studies [30] meets this mission. Among them, 18 studies are targeted, and the remaining 22 studies are untargeted. The panel of potential metabolites is based on the frequency of these metabolites that appear in the publications (Table 6). The common roles of Warburg effect and metabolic reprogramming in these two cancer types are obvious. Similar trend is also obvious in endometrial cancer. It is anticipated that endometrial cancer may share similar metabolomic character of Warburg effect, since endometrial cancer is common in obese, insulin resistance female (data not shown).

9.7. Type 2 diabetes is a common soil cultivating cardiometabolic disease and cancer

It is worthwhile comparing the similarity and characteristic metabolomic profiles between prostate and breast cancers. Warburg effect-related metabolites are common to both cancer types (Tables 5 and 6). As mentioned, a metabolomic study using stored blood samples (12-year storage) from a Framingham study indicates that 5 amino acids (Val, leu, Ile, Phe, and Tyr) are elevated in patients who eventually develop type 2 diabetes [10].

More precisely, type 2 diabetes, even in prediabetic stage, is a common soil cultivating cardiometabolic disease [23] and several types of cancer, including prostate, breast, and endometrial cancers [26] (Table 4). It is helpful that these types of cancer patients may obtain better therapeutic outcome, if their insulin resistance, obesity, and type 2 diabetes are well controlled. More clinical intervention studies are needed.

Table 6. High frequency metabolic biomarkers related to breast cancer diagnosis. Metabolites, up or down in concentrations, are arranged by ranking (metabolites/number of hits in literature/biospecimens in order).

Metabolites	Number of hits in literature	Biospecimens
Tyrosine	12	Plasma, serum, urine, saliva, tissue
Alanine	11	Plasma, serum, urine
Glutamic acid	10	Plasma, serum, urine, saliva, tissue
Valine	10	Plasma, serum, urine, saliva
Phenylalanine	9	Plasma, serum, urine, saliva, tissue
Glutamine	9	Plasma, serum, saliva, tissue
Lysine	9	Plasma, serum, saliva
Isoleucine	8	Plasma, serum, urine, saliva
Histidine	7	Plasma, serum, saliva, tissue
Choline	7	Plasma, serum, saliva, tissue
Glycine	6	Plasma, serum, urine, saliva, tissue
Arginine	6	Plasma, serum, saliva
Asparagine	6	Plasma, serum, urine
Proline	6	Plasma, serum, saliva
Serine	5	Plasma, serum, saliva
Creatine	6	Plasma, serum, urine, tissue
Leucine	6	Plasma, serum, urine, saliva
Tryptophan	6	Plasma, serum, urine
Lactate	6	Plasma, saliva, tissue
Threonine	5	Plasma, serum, urine, saliva
Taurine	5	Plasma, serum, saliva, tissue
Glucose	5	Plasma, serum, urine, tissue
Aspartic acid	4	Plasma, serum, saliva, tissue
Stearic acid	4	Plasma, serum
Ornithine	4	Plasma, serum, saliva
Cysteine	4	Plasma, serum, urine
Glycerophosphocholine	4	Plasma, serum, saliva, tissue
Pyruvate	3	Plasma, serum
Linoleic acid	3	Plasma, serum
Palmitic acid	3	Plasma, serum
Uracil	3	Plasma, serum, urine
Urea	3	Plasma, urine

a. Warburg effect-related metabolites are marked in **bold phase**, BCAAs are ***italic phase*** , and aromatic amino acids are in **bold** and ***italic phase*** . For example: ***glucose***, ***leucine***, and ***phenylalanine***.
b. The biospecimens of serum, plasma, urine, tissue, and saliva are used. Metabolites from serum or plasma may give similar trend. However, their concentrations in serum and plasma may be slightly different. Metabolomic findings obtained from tumor tissue and serum/plasma origins can be powerful biomarkers.
c. Similarity and differences between prostate cancer and breast cancer can be compared between Tables 5 and 6.

10. Conclusion

As a conclusion remark, integration of multiomics strengthens the power of systems biology in precision medicine. Metabolomics, from information to knowledge, enhances the advances in systems biology, translational medicine, and precision medicine (Table 7). The potential of integrated

Table 7. Metabolomics from information to knowledge in systems biology, translational medicine, and precision medicine.

1. **Systems biology**
   a. Top-down; b. global; c. unbiased (or less-biased)
   d. Semi-quantitative (LC-MS) and quantitative (NMR)
2. **Translational medicine**
   a. Common platform from basic to clinical medicine
   b. Biomarker discovery: Portfolio of biomarkers
   c. Key platform technology in precision (personalized) medicine
3. **Integration of omics in precision medicine**
   a. Genomics (phenotyping) and epigenomics
   b. Proteomics
   c. Metabolomics (genotyping)

omics in cancer research deserves the greatest attention.

A problem with systems biology is that each level of biological organization and control, namely genomics, gene expression, protein expression, and metabolism, operate on a different time domain and therefore it is difficult to find causal linkages. Besides, environmental risk factors and lifestyle (epigenetic risk factors) may influence metabolism, making it more difficult to understand their effects and underlying mechanisms, from gene-related outcomes to pathophysiological disturbances (genotyping to phenotyping). It is challenging to design multiomics-based studies to answer these questions.

Further studies on integrated omics and causal correlations with the downstream phenotypes, also called disease landscape, are most rewarding in promoting precision medicine. Metabolomics is a powerful platform technology in many research directions of life science. From molecular cell biology to systems biology (Table 7), the incorporation of metabolomics in modern biomedical studies is essential.

Conflicts of interest

The authors declare that they have no financial conflicts of interest.

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