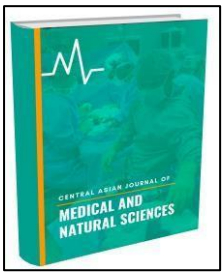

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Article

Metabolic Biomarkers in Cancer: Linking Metabolism to Tumor Progression and Therapeutic Targets

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Abstract: Cancer is a multifaceted disease characterized by profound metabolic reprogramming, which enables tumor cells to sustain rapid proliferation, evade apoptosis, and adapt to microenvironmental stresses. Metabolic biomarkers have emerged as critical tools for understanding tumor biology, aiding in early diagnosis, monitoring disease progression, and guiding therapeutic interventions. This review explores the role of metabolic biomarkers in linking altered cellular metabolism to tumor progression and therapeutic targeting. Hallmarks of cancer metabolism, such as the Warburg effect, glutaminolysis, and lipid metabolism dysregulation, produce distinct metabolic byproducts that serve as potential biomarkers. Key metabolites, including lactate, glutamine, and lipid derivatives, reflect the metabolic demands of tumor cells and their interaction with the tumor microenvironment. Advances in metabolomics and imaging techniques have facilitated the identification of these biomarkers, providing insights into tumor heterogeneity and metabolic vulnerabilities. Moreover, metabolic biomarkers are increasingly being utilized to predict treatment response and resistance. For instance, elevated levels of lactate and hypoxia-inducible factor-1α (HIF-1α) correlate with poor prognosis and resistance to conventional therapies. Targeting metabolic pathways, such as glycolysis inhibitors or glutaminase inhibitors, has shown promise in preclinical and clinical studies, underscoring the therapeutic potential of disrupting tumor metabolism. This review highlights the clinical utility of metabolic biomarkers as diagnostic and prognostic tools, while also emphasizing their role in developing targeted therapies. By integrating metabolic profiling into precision oncology, these biomarkers hold the potential to improve patient outcomes and personalize cancer treatment strategies. Further research is essential to validate their application across diverse cancer types and therapeutic settings.

Keywords: Metabolic Biomarkers, Cancer Metabolism, Tumor Progression, Therapeutic Targets, Metabolomics, Precision Oncology

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1. Introduction

The metabolic profile of cancer is increasingly seen as the next biomarker frontier. Metabolic alterations in tumors are culminations of oncogenic signaling and are intrinsically connected with tumor progression and therapeutic outcomes. The last two decades have seen major advancements in the research of tumor metabolism, and the field has garnered interest from academic and industry participants who are in search of novel targets and companion diagnostics. For patients alone, research in this field promises to mitigate terminal outcomes of late-presenting cancer by broadening the set of biomarkers used for cancer detection, staging, progress monitoring, and understanding underlying biology. Metabolism in cancer is a complex web of interconnected pathways, and

identifying promising biomarkers that can be most beneficial for patient use is critical. In this essay, we will summarize various metabolic pathways that are altered in cancer and aim to discuss how studying these pathways is critical for personalizing cancer therapies for patients [1], [2], [3]. We will focus on techniques for the discovery of metabolic biomarkers and discuss in detail two metabolic pathways that have been the focus of cancer research – reprogramming of glycolysis and reductive glutamine metabolism. Metabolic reprogramming is one of the hallmarks of cancer, and defining the metabolic profile of tumors can be of great use in refining precision medicine strategies for patients. Metabolic reprogramming is the process by which cancer cells alter their metabolic profile to maintain high proliferation and survival rates. Metabolic reprogramming leads to high rates of glucose and glutamine uptake and results in their preferred catabolism to lactate and acetyl-CoA, respectively. These precursors can be further utilized in macromolecule synthesis for the formation of two new daughter cells and maintaining the proliferative potential of the cancer cell [1], [2], [3], [4], [5].

Metabolic Reprogramming in Cancer Cells

The ability to adapt cellular metabolism to various environmental cues is a hallmark of cancer that allows tumor cells to undergo the uncontrolled proliferation necessary for such a disease to take hold, spread, and become established at secondary sites. One of the most pivotal metabolic shifts associated with aberrant energy metabolism is the metabolic switch from the energy-efficient oxidative phosphorylation to glycolysis, known as the Warburg effect or aerobic glycolysis. In cancer, there is substantial routing of glycolytic intermediates into alternative pathways to not only replenish reduced levels of glycolytic intermediates but also to generate substrates and reducing equivalents necessary for building biomass and combating toxic metabolites. This shift in glycolytic intermediates feeds into the major cellular energetics: anabolic versus catabolic processes, which overrides the concept that cancer cells operate a less efficient ATP production process via glycolysis [6], [7], [8], [9].

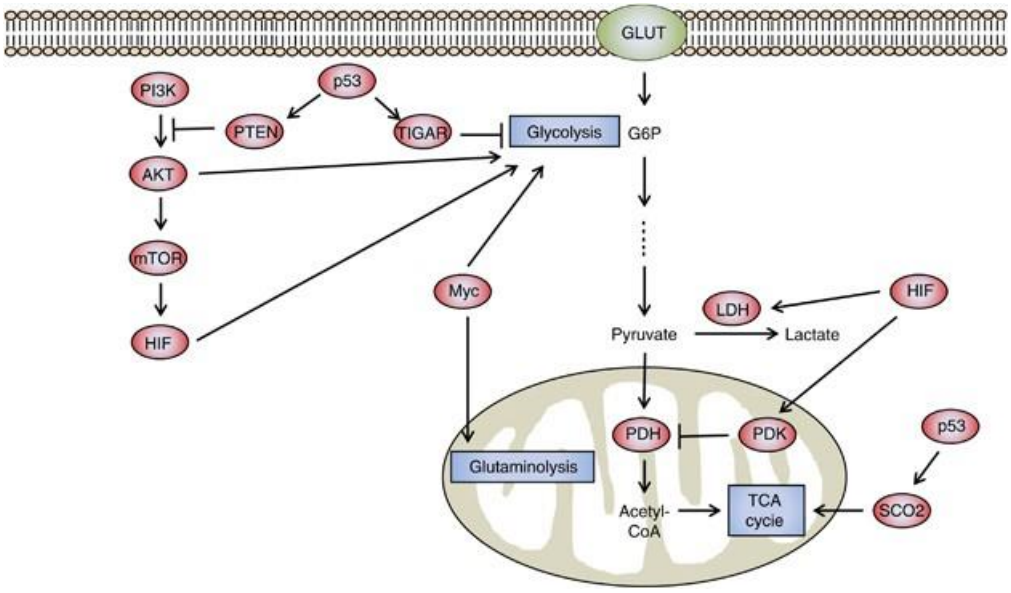

Figure 1. Cancer cell metabolism pathways

Fueled by hypoxia, oncogenes, tumor suppressors, and cellular signaling pathways, cancer cells orchestrate various profound changes in their metabolic profile, giving them proliferative capabilities, anchorage-independent growth, immortality, and escape from programmed cell death. More importantly, reprogrammed metabolism provides tolerance to harsh and stressful environments, such as hypoxia and acidosis. Metabolic alterations also offer an advantage for cancer cells to become resistant against various therapeutic strategies, such as radiation and chemotherapy. Metabolism is closely linked to the signaling pathways to facilitate adaptability in the event of internal or external cue changes, aligning it with the cancer hallmarks. For this purpose, cancer cells establish intricate mechanisms of signal trafficking and transduction in response to perturbed conditions, such as mitochondria-dependent metabolic sensors that empty intracellular ATP through phosphorylating targets to restore energy balance. Targeting metabolism and its associated signaling could potentially serve as a principal approach to achieve the potential of cancer therapy [6], [7], [8], [9], [10].

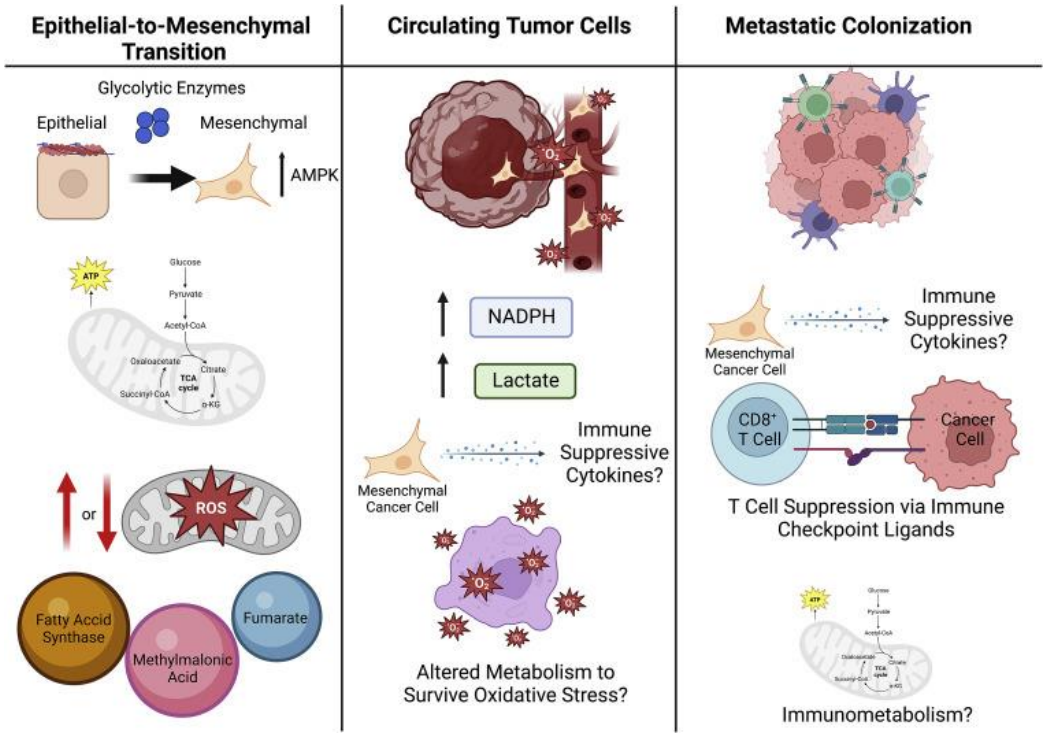

Figure 2. Metabolic alterations in tumor microenvironment

2. Materials and Methods

Metabolic Biomarkers in Different Types of Cancer

Breast Cancer

Breast cancer is one of the most common and well-studied malignancies characterized by a heterogeneous altered metabolism directly impacting the microenvironment within the breast cancer, as well as influencing the development of distal metastasis. Metabolic abnormalities can already be detected in breast cancer cells washed from breast milk and nipple discharge from a high-risk population. Metabolic alterations in breast cancer are often related to unexpected changes in lipid metabolism, both in the expression and activity of lipid-metabolizing enzymes and in the accumulation of androgens. In particular, the derangements of enzymes involved in lipid biosynthesis fatty acid

synthase, acyl-CoA synthetase, and ATP citrate lyase—correlate with known prognostic aggressiveness [4], [11], [12], [13].

Lung Cancer

Alterations in amino acid metabolism are more associated with lung cancer than carbohydrate or fatty acid metabolism. For instance, branched-chain amino acid metabolites are related to differences in early-stage tumor aggressiveness, and serine metabolism is associated with castration-resistant prostate cancer. Unlike the proteome, micronuclei in plasma showed changes with the tumor proteome with an early restoration on treatment initiation—potentially yielding a biomarker of treatment response. Additionally, belonging to a common oncogenic pathway, different lung cancer subtypes exhibited similar primary tumor metabolic gene expression levels. In lung adenocarcinoma, altered choline metabolism may be implicated in the development of brain metastases, and there are temporal changes in metabolic fingerprints across tumorigenesis in a preclinical mouse model. Clear cell lung cancer metabolic fingerprints differ from other histotypes, are characterized by deregulation of numerous metabolic pathways, are more heterogeneous than gene expression, and allow prediction of patient clinical outcomes [11], [12], [13].

Colorectal Cancer

In analogy to normal colonic epithelium, in colorectal cancer, the central metabolic pathways are mainly associated with the Warburg phenotype. One subnetwork of genes associated with hypoxia is mainly located within a hypoxia-specific transcription factor complex, while the other subnetworks of cancer-related genes and metabolic activity are co-localized within a ribonucleoprotein complex, leading to a less extended hypoxia-specific transcription factor complex and mostly having an inverse relationship repressing gene expression. Untargeted analysis of primary tumors of all histological stages from patients compared to the control has shown that colorectal cancer metabolomes differ significantly from non-cancerous colon tissue, with most metabolites being more than 1.5 times annotated in the comparison, with a percentage being immune. The metabolic profile of cancer patients, dysplasia of sections, as well as aspects of tumor behavior, such as stage, site, and grade, can be predicted with this panel of metabolites. Results show a significant and increasing alteration of the malignant colonic metabolic phenotype of tumor samples relative to partially tumor-infiltrated mucosa and to control mucosa. A panel of metabolites could serve as a biomarker for CCR stratification from control, adenoma, and adenocarcinoma with an accuracy of 68% and 70% [11], [12], [14], [15], [16].

Breast Cancer

In the context of breast cancer, altered lipid metabolism has long been regarded as a hallmark of aggressive tumors. Many metabolites have some associations with tumor progression or even with patient survival. High levels of plasma phosphocholine and choline-containing compounds have been associated with tumor progression and poor survival in cancer patients. Overall, elevated serum lactate has been significantly associated with poor clinical factors and outcomes in breast cancer, signifying higher tumor proliferation and aggressiveness. Tumors with high glucose uptake are generally associated with a worse clinical prognosis, which is not necessarily associated with energy consumption. Metabolomic studies continue to be integrated into a variety of clinical trials for different breast cancer subtypes using a variety of tissue and fluid sample types. Breast cancer is often regarded as a hormone-dependent cancer with associated metabolic

features. In the ER+ vs. ER- comparison, there were core metabolites that generally had opposite correlations with disease behavior. The activity of PIK3CA, which occurs in over 40% of tumors, is also demonstrated by the pathway intermediates. Over 40 metabolites associated with breast cancer-related pathways did not correlate with ER status, suggesting increased pathways and metabolites that could be targeted in ER+ breast cancer. In conclusion, there are many different alterations in metabolism present in breast cancer, and as technology and knowledge continue to expand, new treatment strategies will likely emerge [17], [18], [19], [20].

Lung Cancer

Metabolic remodeling in lung cancer

Lung cancer is caused by the accumulation of genetic and molecular alterations that promote tumor formation. In recent years, sustained tumor growth and a high proliferative index of lung cancer cells, as well as metabolic adaptations in metabolic pathways that allow cancer cell precursors to maintain their growth characteristics and the development of new blood vessels, have also been observed. In the field of metabolic reprogramming associated with lung malignancies, it is well known that amino acid metabolism has attracted growing interest. In fact, either supplementing glutamine and serine or the glutamine analog reduced the growth of CDKN2A-deficient lung cancer, which may also translate into models of KRAS activation. Finally, it has been shown that lung tumors undergo metabolic adaptations only under conditions of hypoxia, which promote a certain phenotype of this tumor [12], [21], [22].

Use of metabolic biomarkers to design therapeutic strategies for lung cancer

Can we escape the metabolic tensions unique to our lung tumors to design specific therapies? Identification of potential targets unique to each of the metabolic states described could help guide these exciting research efforts. Finally, it is important to note that further studies are needed to determine the links between better-defined metabolic pathways in lung tumors and to study metabolic agents in patients, which may pave the way for potential combination therapies. Metabolic biomarkers could therefore be of great interest in the clinical management of cancer, but have a limited number of clinical translations due to a limited understanding of the influence of the environment. The tumor microenvironment on the metabolism of cancer cells is generally recognized. This focuses on the role of metabolic alterations specifically in lung cancer development, analyzes metabolites from energy metabolism to amino acids, and presents potential biomarkers for lung cancer diagnosis, classification, and prediction [17], [23], [24], [25].

Colorectal Cancer

Compared to the previous subsections, many more papers in this Special Issue addressed colorectal cancer (CRC) as opposed to the more general term of GI. This is likely due to the more developed nature of research into colorectal metabolic changes, thus leading to increased interest in the application of metabolite profiling to CRC. Current knowledge of metabolic alterations in colorectal tumorigenesis focuses on changes in carbohydrate metabolism. Lower levels of butyrate released by gut microbiota have been proposed as a potential biomarker for the progression of colorectal tumors from adenomas to carcinomas. The metabolite increases within CRC can be due to more aggressive cancer cells that survive the hypoxic tumor microenvironment or enhanced activation of the Warburg effect or Crabtree effect at the tumor cell surface. Choline, which is transformed into several cancer-linked metabolites including the membrane component

phosphocholine and pro-potent choline kinase inhibitors, has been most studied in CRC, and high total choline is identified as a promising urine metabolite biomarker for monitoring therapeutic efficacy [21], [26], [27], [28].

The metabolic profiling of early stages of colon cancer adenoma is sparse, limited to short time-frame cancer risk prevention trials and patients who were most likely to have undetected proximal carcinomas at screening. The potential of metabolomic profiling for the detection of early-stage CRC at screening colonoscopy is hindered by the array of methodological challenges in colorectal metabolomics, such as low signal metabolite to noise ratio due to the abundance of amino acids in stools, the need for extensive fractionation and clean-up of samples, the lack of consideration in resolving active cutting serine protease contaminants against metabolic targets, and different types of biofluids and tissues to study. The application of metabolites as adjuvant biomarkers and new drug targets in CRC is "a new frontier in colorectal cancer metabolism." The metabolic pathways that are altered in CRC and the ways in which this metabolic reprogramming can be exploited to improve colorectal cancer treatment using directed metabolic interventions as well as by altering the tumor microenvironment are also discussed [21], [26], [27], [28], [29].

Role of Metabolic Biomarkers in Tumor Progression

Understanding the mechanisms underlying tumor progression is important for developing new therapeutic strategies and identifying new targets. Metabolism is a dynamic and complex set of biochemical processes that produce energy as well as basic components for tumor cell growth and proliferation. The ability of cancer cells to reprogram these metabolic pathways to more aggressive behavior is supported by many experimental studies. Previous investigations have shown how modifications in metabolic pathways are linked with tumor characteristics such as proliferation, evading death, and the ability to promote local network growth, invasiveness, and metastasis. Tumor cells exhibit metabolic alterations distinct from the normal tissue of origin, which also affect the microenvironment, thus promoting the proliferation of surrounding stromal cells [30], [31], [32].

The link between metabolomics and tumor progression lies in understanding the tumor microenvironment. In tumor progression, metabolic profiling is crucial, where less understood and rarer neoplasms are also linked with serum concentrations of metabolic markers. The tumor interacts with metabolites that are being used to promote growth and immune evasion. Such compounds have been shown to impact the tumor microenvironment, promoting angiogenesis, stromal proliferation, and mesenchymal differentiation. Metabolic profiling investigates how a state of systemic inflammation is impacted by the tumor microenvironment. These studies explore how altered electrolyte metabolism may be linked to local excitability, which may also suggest where the tumor is localized. Metabolic profiling may be used to identify high-risk patients and, based on cellular stress metabolites, predict further treatment success. Various electrolytes have been shown to be actionable targets for the metabolic composition of the tumor microenvironment, with ischemia metabolomics correlating with disease stage. Clinical outcomes have verified varying diagnostic capacity in many cancer types; however, a larger dataset would be important to verify these results. Metabolomics therefore appears to represent the local tumor microenvironment and, to a certain extent, correlate with

clinical outcomes. To verify this, cross-cancer research is important in varying metabolic biomarkers and should be performed [17], [23], [30], [31], [32].

3. Results

Metabolic Biomarkers as Predictors of Treatment Response

Most of the standard treatment options that an oncologist can provide will result in some degree of side effects that reflect drug processing in cells and tissues, with the possibility of decreasing or even completely abolishing the cancer-suppressing effect and low overall cancer drug efficacy. Investigating glycolytic, anti-oxidative, and mitochondrial metabolites can shed light on the cell or tissue state regarding drug efficiency via the identification of patients who will respond to the treatment, behave as non-responders, or even develop resistance. Monitoring metabolic alterations on the go will allow for the adaptation of the therapy, increase response to the implemented therapy, and enhance patient survival and quality of life. In concordance with these observations, several studies correlated specific metabolic changes and levels of individual tumor or serum metabolites before the initiation of cancer treatment with the chances of developing treatment resistance and failing to efficiently suppress tumor progression. Long story short, specific metabolites in tumor tissue and serum of patients at diagnosis can serve as biomarkers for poor prognosis and treatment resistance [23], [33], [34], [35], [36].

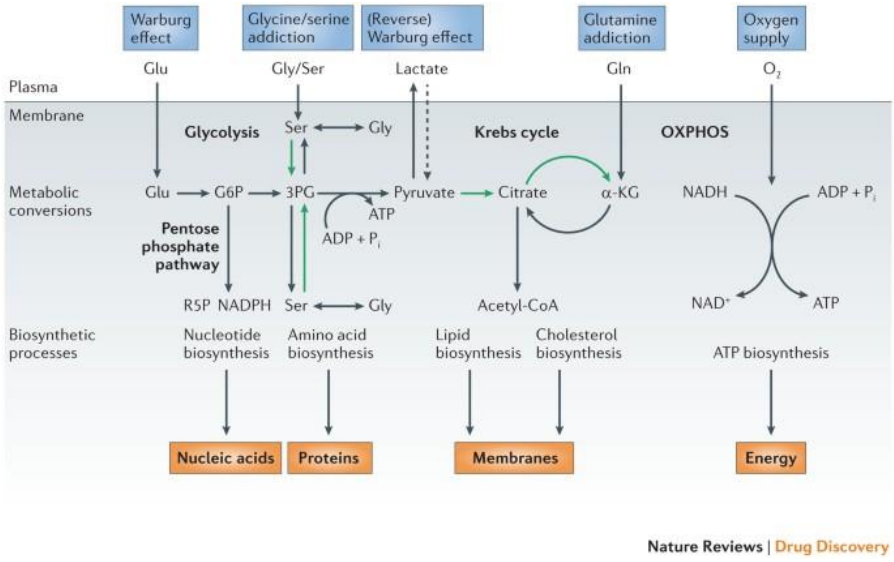

Figure 3. Metabolic targets for cancer therapy

Metabolic changes have been summarized as being responsible for the initiation and dynamic progression of cancer cells that will eventually define the responses of cancer patients to the implemented therapeutic strategies. More importantly, metabolic reprogramming has been suggested to represent the Achilles' heel of cancer, highly required to sustain an increased nutrient and oxygen demand and cope with cell division and differential cellular function; none of these can be simply satisfied. Treatments, therefore, aim to inhibit metabolic pathways so that the formation of cancer characteristics is suppressed. Many reports and reviews have emphasized the potency of altered metabolism in some cancer cells and tissues in predicting both treatment efficacy and the possibility of cancer cells developing resistance towards treatment. Despite the challenges and limitations encountered while translating the research findings suggested

herein into the clinic, a multimodal approach or the addition of altered metabolism to the research findings that served to describe improved diagnosis, prognosis, and prediction would accelerate patients' access to an effective therapeutic strategy [23], [25], [33], [34], [35], [36].

Therapeutic Targeting of Metabolic Pathways in Cancer

Consequently, altering cancer metabolism can reprogram cancer cell physiology and potentially contribute to diminishing cancer growth and spread. Indeed, the current gap can be the effect of cancer therapies based on the potential specific targeting of biological processes that can contribute to slowing down cancer dimensions. This research further identifies the complexity of patients' biology and dynamics; however, we can improve performer identification and stratification and the procedures for testing effective treatment. By doing so, it will be the central element of future and current progress in personalized medicine. Stimulating the immune system could provide the "upper hand" because cancer metabolism and tumor-host interactions physiologically suppress anti-cancer defenses. The therapeutic requirements to inhibit metabolic pathways have been identified. Some research strategies are envisioned for the analytical capacity and reliability of measuring metabolic fluxes and predicting how cellular physiology will respond to metabolite starvation. Currently, there are two principal ways of interfering with metabolic fluxes: small molecules and biological compounds. Additionally, a great opportunity opens up for the identification of new therapeutic targets and the establishment of innovative approaches for the treatment of complex multifactorial diseases such as cancer and neurodegeneration. Finally, the development of new possible medical products, such as combination drugs, poses a number of regulatory challenges and identifies issues for the foreseeable future [37], [38], [39], [40].

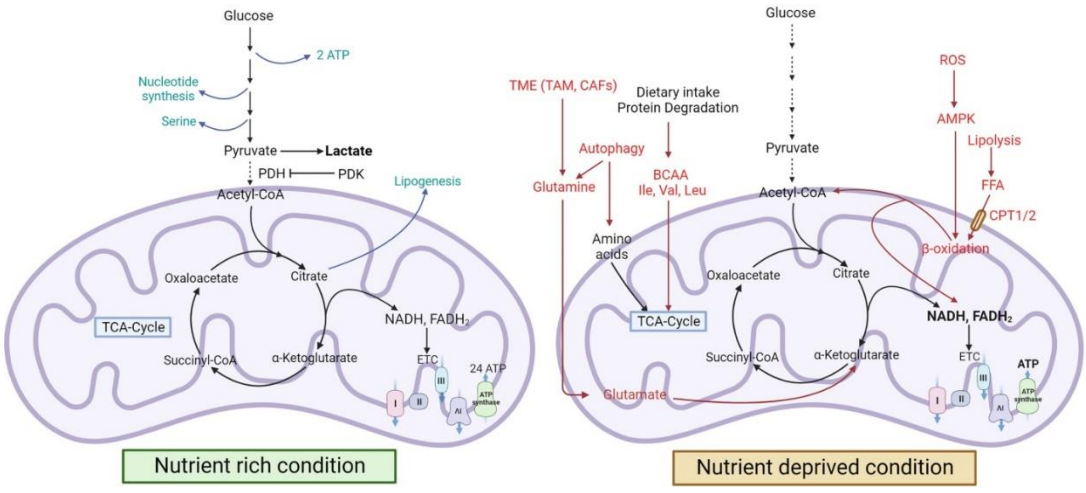

Figure 4. Therapeutic targeting of metabolic pathways

4. Discussion

Current Challenges and Future Directions in Metabolic Biomarker Research

Challenges are encountered along every step in metabolic biomarker discovery in cancer. As there are no standardized metabolic biomarkers, diverse technologies are used, ranging from NMR spectroscopy, liquid and gas chromatography with a plethora of mass spectrometers that have varying sensitivity and coverage ranges, and finally to targeted approaches, such as antibody arrays. It is evident that the methodologies differ significantly between studies and, hence, the ability to integrate findings is severely

hampered. Furthermore, the development of robust informatics tools and algorithms to ensure meaningful data analysis is required to improve standardization and, subsequently, the reproducibility of metabolomic profiling. Finally, the transition of biomarkers identified using these technologies to clinical application creates new challenges in terms of regulatory approval. Future Directions. There are several robust methods that need further validation and phenotype stratification to ensure a more seamless cancer treatment paradigm for the patient, and the degree of integration of metabolomics with genomics and proteomics approaches is a potential for innovative breakthroughs. Large-scale clinical initiatives illustrate the commitment by clinicians, researchers, and industry to investigate and exploit combinations of metabolic, genetic, and protein markers of cancer. These should be powerful studies that combine the diverse expertise of participating researchers and should pave the way for the development of what are known as molecular signatures, which may include some of the metabolic biomarkers outlined in the review. Recent technological developments, such as in vivo magnetic resonance spectroscopy, may help the transition of biomarkers from identifying to imaging techniques, which inform treatment more directly. Crucially, these approaches also involve clinicians, research scientists, and industry in a collective approach that should enhance biomarker discovery, validation, and application at a greater rate than if pursued in a discipline-specific manner. One major technical advance that may strengthen metabolic biomarker development is the relatively recent ex vivo high-resolution magic angle spinning, which could offer significant improvements in terms of signal resolution and multiple biomarker identification. These ongoing technical and clinical developments in the application of ex vivo HR-MAS may well tip the balance in favor of metabolic biomarker identification if spatial resolution within such tissue is linked to molecular searchable databases. In reality, there will never be one revolution that will change the way metabolomics will be used in medical research. Rather, a series of small, incremental, evolutionary steps will be needed from a wide variety of platforms, search strategies, and validation techniques, overlapping with input from concomitant omics data, such as genomics and proteomics, to increase global impact on the quality of healthcare outcomes. In doing so, metabolomics and the identification of cancer metabolic biomarkers will have made a substantial difference to the future of medicine [23], [24], [41], [42].

5. Conclusion

Metabolism is one of the hallmarks of cancer, and its deregulation allows tumor cells to acquire an aggressive phenotype. In the previous sections of the manuscript, we have assessed the main pathways that are dysregulated in various tumor types as well as the metabolic biomarkers that have a clear correlation with tumor progression. Specifically, we have analyzed the possibilities that these metabolites could offer to improve the early detection of cancer and to help in prognostication in an attempt to guide different therapeutic strategies, including personalized therapies. Overall, the use of metabolic profiling in clinical practice could revolutionize the way in which cancers are approached with a purpose to optimize patient care. Metabolic profiling may represent a significant breakthrough, although current data should be further validated and backed up by prospective multicenter studies before we see metabolic biomarkers used in the clinical setting. Moreover, one important aspect of clinical research is the problem

of accessing the proper tissue samples. Blood-based assays may solve this problem since it is easier to obtain blood samples, and they are more representative of the tumor heterogeneity, containing all the circulating tumor cells. However, a combination of omics approaches, including proteomics and metabolomics, may solve the existing knowledge gap and help to retrieve important information regarding tumor biology. Therefore, there is a need for close communication between basic scientists and clinicians in order to further translate metabolomics advances to the everyday clinic in a multidisciplinary landscape. The emerging potential of metabolomics is quickly moving towards clinical application in personalized oncology. In conclusion, understanding the intricate pathways of tumor metabolism will lead to more effective strategies in the clinical management of cancer.

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Declaration of competing interest

The authors say they don't have any known personal or financial relationships or financial interests that could have seemed to affect the work in this study.

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