INTRODUCTION

Prostate cancer (PC) is the most frequently diagnosed malignancy among males worldwide. In recent years, there has been a need to find alternative methods for the early diagnosis of PC. Evidence indicates that metabolic dysfunction is a characteristic feature of PC carcinogenesis, with various metabolites acting as biomarkers of tumor growth. Metabolomics is a new science that has emerged at the intersection of molecular biology, biochemistry, and genetics. The complete set of substrates and metabolic products is a metabolic profile, or metabolome. The PC metabolome comprises substances formed as a result of metabolic changes in response to the occurrence of a malignant process in the prostate gland. We have obtained unique data on metabolic changes that allow us to rethink the carcinogenesis of PC. Research on the metabolome opens up new opportunities for the early diagnosis and treatment of PC, with implications for its prognosis.

Key Words: Prostatic neoplasms, Metabolomics, Metabolome, Biomarkers, Prostatic hyperplasia

Grant/Fund Support: This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflicts of Interest: The authors have nothing to disclose.
and reduce unnecessary treatment and diagnostic measures. The problem of the inpatient or outpatient diagnosis of PC, as well as differentiation from benign prostatic hyperplasia (BPH), is currently a key issue in the world of uro-oncology [4]. The most common methods of early diagnosis are measurements of the level of prostate-specific antigen (PSA) in the blood and digital rectal examination (DRE) of the prostate gland. Despite the high level of sensitivity of methods for determining PSA and its fractions in neoplasms, elevation of this marker is also characteristic of BPH, which makes it impossible to reliably differentiate clinically significant forms of PC from non-malignant prostate diseases based on this indicator alone [5]. DRE, a physical diagnostic method based on palpation, can determine the presence of pathological formations of the prostate gland only if they are sufficiently large. Taking these characteristic features into account, identifying the early stages of PC is very difficult. Unfortunately, measurements of PSA levels and DRE are not able to meet the current needs of early diagnosis in the framework of highly specialized cancer care. Evidence now indicates that metabolic dysfunction is a characteristic feature of PC carcinogenesis [6], while various circulating metabolites act as biomarkers of tumor growth and prognostic markers of the aggressiveness of the neoplastic process [7,8]. The study of the metabolic bases of carcinogenesis in prostate tumors and the determination of the leading substrates in the biochemical profiles of patients will enable new advances in the screening, early diagnosis, and treatment of PC [9].

**METABOLOME AND METABOLOMICS: RESEARCH HISTORY**

Metabolomics is a novel scientific approach that emerged at the intersection of molecular biology, biochemistry, and genetics. Along with genomics, transcriptomics, and proteomics, it is one of the modern “chemical” disciplines in the system of studying biological processes at the subcellular level. Metabolomics and other “omic” sciences focus on determining the molecular genetic profile in certain physiological and pathological processes [10]. Metabolomics identifies and analyzes metabolites formed during the vital activity of cells (exogenous and endogenous molecules less than 1.5 kDa in size) and detected in body fluids and secretory secretions [11]. The complete set of substrates, intermediates, and metabolic products is a metabolic profile, or metabolome, and the organization and grouping of these substances can be performed at the cellular, tissue, and organizational levels [12,13].

The history of the study of the metabolome began in the late 1940s, when a group of researchers led by Roger Williams first developed the concept of a unique metabolic “portrait” for each person. Scientists performed paper chromatography of urine and saliva to determine the distribution of molecules of substances in these media. Based on the results of the work, the authors concluded that substrates and metabolic products are unique for each individual organism, and the distribution and ratio of components of biological media are not stable and dynamically change over time [14]. In addition to establishing the metabolome and its uniqueness at the level of the body, the researchers compared metabolic patterns between individuals with alcohol dependence and psychiatric patients. The researchers concluded that there was a significant difference in the chromatography results between the experimental groups, despite the qualitative nature of the analysis. A real breakthrough in the study of the metabolome occurred in the early 1970s, when methods for the quantitative study of liquid media molecules were developed [15]. In 1971, Horning coined the term “metabolic profile” [16], following the results of a fundamental study by Dalgliesh et al. [17], which demonstrated high-precision measurements of components of biological fluids and tissue structures using gas chromatography-mass spectrometry. In 2007, the human metabolome was fully investigated using nuclear magnetic resonance spectroscopy and mass spectrometry. Currently, the current version of the Human Metabolome Database contains information on more than 2,280 metabolites of medicines, 25,000 metabolic pathways in pathologies, 28,000 metabolites of food components and additives [18]. Mass spectrometry and nuclear magnetic resonance spectroscopy are currently the most common methods of metabolomic studies. Mass spectrometry is combined with liquid/gas chromatography or capillary electrophoresis. Each method has its own advantages and disadvantages, making it important to consider the physicochemical properties of the studied molecules [19,20].
PHYSIOLOGICAL METABOLISM IN PROSTATE CELLS

A key role in the metabolic processes of body cells is the provision of energy substrates for all biochemical reactions. It is also important to note that the choice of a specific energy formation pathway often determines cellular function. Healthy prostate cells derive their energy from adenosine triphosphoric acid (ATP) molecules, which are produced during anaerobic glycolysis. Normal prostate epithelial cells exhibit a distinctive metabolic profile, characterized by the accumulation of zinc and citrate molecules [21]. The accumulation of zinc and citrate is necessary for the normal function of spermatozoa and the achievement of physiological parameters in sperm cells [22,23]. Zinc inhibits the enzyme mitochondrial aconitase, which is involved in the conversion of citrate into isocitrate, contributing to the accumulation of citrate and the cessation of further reactions in the tricarboxylic acid cycle. The use of anaerobic glycolysis as a faster way to obtain energy sources via the high-energy bonds of ATP molecules allows cells in a healthy prostate gland to be in dynamic equilibrium [24].

THE PC METABOLOME: FEATURES AND SIGNIFICANCE IN CARCINOGENESIS

The metabolome of PC consists of substances produced through metabolic changes in response to the development and progression of a malignant process in the prostate gland. Differentiating the PC metabolome from the body’s general metabolism is crucial for accurately interpreting research results and diagnostic procedures. Blood serum or urine is typically used to study these biochemical changes, although efforts are currently being made to develop methods for analyzing prostate tissues [25].

The basis for changes in the metabolome in PC is formed by disruptions of physiological and biochemical processes in prostate cells [26-28]. As a result of malignant transformation, zinc levels decrease, which leads to the activation of mitochondrial aconitase and conversion of citrate to isocitrate [29,30]. This rearrangement triggers the tricarboxylic acid cycle and dramatically changes the metabolism of PC cells. As a result, tumor cells acquire the ability to obtain more energy in the form of ATP molecules through cellular respiration with aerobic glycolysis, or, more often, to use citrate transformation for de novo synthesis of acetyl-coenzyme A and fatty acids [31]. These features make PC unique and distinguish this pathology from many other tumors (Fig. 1).

The high oxidative capacity and glucose independence demonstrate an exception to the Warburg effect [29,32]. Zinc plays a crucial role in the malignant transformation of prostate cells. Beyond altering energy processes, this element influences the proliferative and invasive activities of PC

Fig. 1. The main metabolic changes of PC. TCA, tricarboxylic acid; G6P, glucose-6-phosphate; Ac-CoA, acetyl-coenzyme A.
A simultaneous decrease in zinc and citrate levels is associated with the progression and metastasis of PC [30,34]. PC is also characterized by a decrease in spermine in organ secretions, which multiple studies have established as being associated with an increase in the aggressiveness of the disease [35].

The past decade has seen a significant increase in the number of studies investigating the metabolic profile of PC using various platforms [10,22,23,31,36,37]. These studies have identified metabolites characteristic of PC, among which the main ones are sarcosine and choline in blood plasma and urine [38]. Among other compounds included in the PC metabolome, Franko et al. [39] described arginosuccinate, arginine and proline. These substances are products of the urea cycle and were significantly elevated in patients with PC compared to those with BPH. In another study, Vykoukal et al. [40] demonstrated a correlation between increased levels of fumarate (as a result of activation of the oncogenic signaling pathways HIF-1α and nuclear factor-kappa B) and low survival rates in PC patients. The researchers also noted a link between elevated concentrations of sphingolipids and caveolin-1 in blood plasma and high aggressiveness in the clinical course of PC. Caveolin-1 modifies the metabolism of fatty acids by activating the transformation of sphingomyelins into ceramide derivatives. These processes favorably increase energy resources in cells and contribute to greater activity of the neoplastic process.

A number of studies conducted more detailed analyses of the metabolism of sarcosine and its relationship with the development of PC. One of the first major studies on this compound was the work of Sreekumar et al. Scientists using liquid and gas chromatography, as well as mass spectrometry, conducted metabolic profiling of biosimilars of patients with PC and healthy people in the control group. An analysis of blood serum, urine, and prostate tissues showed a slight increase in the levels of uracil, kynurenine, glycerin-3-phosphate, leucine, and proline in patients with PC. A significant increase in the level of sarcosine in biological samples was noted in metastatic PC compared with the control group, as well as in localized PC compared to BPH [41]. Subsequently, many studies explored the correlation between high levels of sarcosine in metabolic profiling and the presence of PC, but without providing a clear conclusion. For instance, in the work of Jentzmik et al. [42], no correlations were found between the sarcosine concentration and the presence of a malignant process in the prostate gland, taking into account the Gleason score. Contradictory results were also demonstrated in some other studies [43,44]. Yousefi et al. [45] studied sarcosine levels in 67 patients, including 25 healthy individuals (control group), 23 with established BPH, and 19 with PC. A significant increase in sarcosine in serum and urine was noted in patients in the PC group. A lower level was observed in the BPH group, and the lowest was noted in the control group. The most frequent change reported in studies conducted over the past 5 years is a significant decrease in citrate levels in prostate tissue [39]. This loss of the ability to accumulate citrate leads to profound changes in the energy metabolism of prostate cells, wherein prostate cells begin to use citrate in the tricarboxylic acid cycle more efficiently than normal prostate cells. Furthermore, PC tissues have a low level of spermine in the prostate fluid, which contributes to their aggressiveness [35]. They are characterized by high levels of choline, sarcosine [38], taurine, myo-inositol, and pyruvate kinase M2 [46]. Elevated levels of other key metabolites of the tricarboxylic acid cycle—namely, succinate, malate, and fumarate [47]—were also frequently mentioned in review studies. An increase in malate and fumarate levels also correlated with the Gleason score and tumor stage [48]. The current picture of uncertainty and inconsistency with respect to only one metabolite indicates the need to further improve the methods of preparing biological samples and technical equipment, as well as the methods of analyzing the data obtained. Currently, many studies are being conducted with the goal of identifying patterns in metabolic rearrangements in PC and determining the “typical” metabolome in this pathology, which will certainly contribute to the emergence of new methods of diagnosis and treatment.

**PROSPECTS FOR INTEGRATING METABOLIC PROFILING IN THE DIAGNOSIS AND TREATMENT OF PC**

The distinctive advantage of metabolomics, in comparison with other “omic” sciences, lies in its ability to reflect dynamically changing parameters of the body with the
formation of a specific phenotype. The study of the metabolome can allow not only to identify biomarkers of PC, but also to conduct metabolic differentiation of various clinical phenotypes with subsequent stratification of patients to determine tactics for diagnosis and treatment. Advances in understanding the pathological metabolism of PC cells have made it possible to perform metabolic imaging of PC. Due to the absence of dependence on glucose and glycolysis, PC cells have a low avidity to fluorodeoxyglucose (FDG), which is used in $^{18}$F-FDG positron emission tomography/computed tomography [49]. Another example of the introduction of metabolic profiling is the study of metabolic columns of tissues during trepan biopsy of the removed prostate after radical prostatectomy to stratify patients by risk groups or predict treatment results. Of course, one of the main areas of clinical application of metabolomics will be the determination of PC biomarkers. Despite the contradictory results of studies on the reliability of sarcosine use for PC verification, other amino acids and their derivatives that can serve as potential markers of PC are currently being studied [50,51].

One of the areas of application of metabolomics is the identification of risk factors for PC. Tumor occurrence and progression are associated with oncogenic mutations in the genetic material of the cell, which are caused by exogenous and endogenous factors. DNA damage causes changes in metabolism. Each aspect of genetic damage is characterized by characteristic metabolic rearrangements, which are caused both by the synthesis of abnormal amino acids and proteins, and by epigenetic shifts in the regulation of polypeptide synthesis [36]. Metabolomics can also be integrated into the process of creating drugs that affect the metabolism of PC. Exposure to key molecules in the processes of carcinogenesis and metastasis will make it possible to destroy the pool of malignant cells at an early stage [52,53]. Epidemiological data show that obesity and excessive calorie intake are associated with a higher incidence of PC [54]. Patients with PC often have metabolic syndrome, which is characterized by hyperinsulinemia, hypertension, central obesity, loss of muscle mass, and dyslipidemia. Dyslipidemia is of major importance for metabolic changes, which may play a role in the carcinogenesis of PC. Lipids, including fatty acids, phospholipids, and cholesterol, play a crucial role in the progression of PC. There is a functional relationship between cholesterol metabolism and the progression of PC. High levels of circulating cholesterol are positively associated with the development of PC [37], and cytosolic lipid droplets containing cholesterol esters are associated with its aggressiveness [55].

**CONCLUSION**

The integration of metabolomics into practical medicine opens up new opportunities for the comprehensive diagnosis and treatment of malignant neoplasms. PC is one of the most urgent problems of modern oncology and urology, and studies of the metabolism of this pathology expand the boundaries of understanding the neoplastic transformation of healthy prostate cells. Features of molecular regulation of intracellular processes make PC a metabolically unique disease that does not have the classic biochemical abnormalities that are characteristic of most solid neoplasms. Studying the PC metabolome will identify new biomarkers of the disease, improve the diagnosis in its early stages, and create the foundation for the development of new targeted drugs. Currently, there is an active increase in the number of metabolomic studies of PC, revealing new mechanisms of carcinogenesis. The active use and development of metabolomics in conjunction with other “omic” disciplines will allow us to rethink the views on the diagnosis and treatment of PC.

**NOTES**

- **Author Contribution:** Conceptualization: VNP, MFU, MRB; Data curation: MFU, MRB; Formal analysis: MFU, MRB; Methodology: VNP, MFU, MRB; Project administration: MFU, MRB; Visualization: MRB; Writing - original draft: MRB, OSA; Writing - review & editing: MRB, OSA.

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