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Review Article

Integral role of metabolic profiling in patients with prostate cancer

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ABSTRACT

Prostate cancer is the most diagnosed malignant neoplasm among males worldwide. Over the past few years, there has been a need to find alternative methods for early diagnosis of prostate cancer. There is evidence that metabolic dysfunction is a characteristic feature of the carcinogenesis of prostate cancer, with various metabolites acting as biomarkers of tumor growth. Metabolomics is a young science that arose at the junction of molecular biology, biochemistry and genetics. The complete set of substrates and metabolic products is a metabolic profile, or metabolome. The metabolome of prostate cancer is formed by substances formed as a result of metabolic changes in response to the occurrence of a malignant process in the prostate. Unique data on metabolic changes have already been obtained, allowing us to rethink the carcinogenesis of prostate cancer. The study of the metabolome opens up new opportunities for early diagnosis, prognosis and treatment of prostate cancer.

Keywords: prostate cancer; metabolomics; metabolome; biomarkers of prostate cancer; benign prostatic hyperplasia.

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Интегральная роль метаболического профилирования у пациентов с раком предстательной железы

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АННОТАЦИЯ

Рак предстательной железы — самое диагностируемое злокачественное новообразование среди лиц мужского пола во всем мире. За последние несколько лет возникла необходимость в поиске альтернативных методов ранней диагностики рака предстательной железы. Имеются данные, что метаболическая дисфункция является характерной особенностью канцерогенеза этого заболевания, при этом различные метаболиты выступают в качестве биомаркеров опухолевого роста. Метаболомика — молодая наука, возникшая на стыке молекулярной биологии, биохимии и генетики. Полный набор субстратов и продуктов метаболизма представляет собой метаболический профиль, или метаболом. Метаболом рака предстательной железы формируют вещества, образующиеся в результате биохимических изменений в ответ на возникновение злокачественного процесса в предстательной железе. Уже сейчас получены уникальные сведения о метаболомных особенностях, позволяющих переосмыслить канцерогенез заболевания. Изучение метаболома открывает новые возможности для ранней диагностики, прогнозирования и лечения рака предстательной железы.

Ключевые слова: рак предстательной железы; метаболомика; метаболом; биомаркеры рака предстательной железы; доброкачественная гиперплазия предстательной железы.

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ЭКО•ВЕКТОР

INTRODUCTION

Prostate cancer (PCa) is the most diagnosed type of cancer in men and is most commonly found in patients over the age of 50. Currently, this disease is the leading cause of cancer-related deaths in men around the world [1]. In addition to the deterioration of somatic parameters associated with the presence and progression of a neoplastic lesion, early-stage PCa has a significant impact on the quality of life and psychological status of patients [2]. Although there are population and geographic differences in morbidity and mortality, evidence-based risk factors for PCa include age, ethnicity/race, and family history. At the same time, dysregulation of carbohydrate and lipid metabolism is a proven predictor of PCa progression with excess fat accumulating in subcutaneous tissue and internal depots [3].

PCa is a clinically heterogeneous disease that manifests with different process activities regardless of its stage. In recent years, the need to find alternative, non-invasive ways to diagnose PCa has increased. During the initial examination, it is very important to assess the prognostic component of the tumor process to improve the management strategy and reduce the number of unnecessary invasive procedures. Currently, one of the key issues in global urologic oncology is the primary or outpatient diagnosis of PCa and its differentiation from benign prostatic hyperplasia (BPH) [4]. The most common PCa screening methods include blood prostate-specific antigen (PSA) testing and digital rectal examination (DRE) of the prostate. Despite the high sensitivity of the methods used to determine PSA and its fractions, elevated PSA is also typical of BPH and does not reliably distinguish clinically significant forms of PCa from "non-malignant" prostate diseases [5]. DRE refers to palpation methods of physical diagnosis, which allows identifying prostate lesions only if they are large enough. Therefore, it is very difficult to detect the early stages of PCa. Unfortunately, the PSA test and DRE do not meet current needs for early detection in highly specialized oncology care. Current evidence suggests that metabolic dysfunction is a hallmark of PCa carcinogenesis [6]. Some circulating metabolites serve as biomarkers of tumor growth and prognostic markers of neoplastic aggressiveness [7, 8]. We can take a new step in the screening, early diagnosis, and treatment of PCa by investigating the metabolic basis of prostate tumors and identifying the leading substrates in the biochemical profiles of patients [9].

UNDERSTANDING METABOLOMICS AND METABOLOME

Metabolomics is an emerging science that spans molecular biology, biochemistry, and genetics. Along with genomics, transcriptomics, and proteomics, it is one of the modern "-omics" disciplines for studying biological processes at the subcellular level. The goal of metabolomics and other -omics is to determine the molecular genetic profile of physiological and pathological processes [10]. Metabolomics identifies and analyzes metabolites (exogenous and endogenous molecules weighing less than 1.5 kDa) produced as a result of cell activity and detected in body fluids and secretions [11]. The complete set of substrates, intermediates, and metabolites is called a metabolic profile or metabolome, and they can be grouped at the cellular, tissue, and organismal levels [12, 13].

The history of metabolomics began in the late 1940s when a group of researchers led by R. Williams developed the concept of unique individual metabolic "portrait." Urine and saliva were paper chromatographed to determine the distribution of molecules found in these media. It was concluded that substrates and metabolites are unique for each individual organism, and the distribution and ratio of components of biological media are not stable and change dynamically over time [14]. In addition to determining the metabolome and its uniqueness at the organism level, the metabolic patterns in alcoholic and psychiatric patients were compared. Despite the qualitative nature of the analysis, there was a significant difference in the chromatographic results between the experimental groups. A real breakthrough in metabolomics occurred in the early 1970s with the advent of quantitative methods for molecular assays in liquid media [15]. In 1971, E. Horning and M. Horning introduced the term "metabolic profile" [16], based on the results of fundamental research by C.E. Dalgliesh et al. [17], which demonstrated the high-precision measurement of components of biological fluids and tissue structures using gas chromatography–mass spectrometry. In 2007, with the advent of nuclear magnetic resonance spectroscopy and mass spectrometry, the human metabolome became completely understood. The current version of the Human Metabolome Database contains information on more than 2,280 drug metabolites, 25,000 pathological pathways, and 28,000 metabolites of food components and additives [18]. Mass spectrometry and nuclear magnetic resonance spectroscopy are currently the most widely used methods in metabolomics. Mass spectrometry is combined with liquid/gas chromatography or capillary electrophoresis. Each method has its own advantages and disadvantages depending on the physicochemical properties of the molecules being analyzed [19, 20]. This requires more careful planning of the research model.

PHYSIOLOGICAL METABOLISM IN PROSTATE CELLS

A key role in the metabolic processes of every cell in the body is to provide energy substrates for biochemical reactions. It should be noted that a way to produce

energy often determines how cells function. Adenosine triphosphate (ATP) molecules produced during anaerobic glycolysis are the energy source for healthy prostate cells. Normal prostate epithelial cells have a unique metabolic profile characterized by accumulating zinc and citrate molecules [21]. Zinc and citrate accumulation is required for sperm cells to function and achieve physiological sperm parameters [22, 23]. Zinc inhibits mitochondrial aconitase, which is involved in the citrate conversion to isocitrate, promoting citrate accumulation and stopping further reactions in the tricarboxylic acid cycle. The cells of a healthy prostate are dynamically balanced by using anaerobic glycolysis as a faster way to obtain energy sources in the form of macromolecular bonds of ATP molecules [24].

PROSTATE CANCER METABOLOME: CHARACTERISTICS AND ROLE IN CARCINOGENESIS

The PCa metabolome consists of substances produced because of metabolic changes in the body in response to developing and progressing prostate cancer. It is important to distinguish the PCa metabolome from the general metabolome of the body to properly interpret test results and diagnostic procedures. Serum and urine are used to study the biochemical shifts, but some methods are currently being developed for the analysis of prostate tissue [25].

Metabolomic shifts in PCa are driven by impaired physiological biochemical processes in prostate cells [26–28]. Malignant transformation decreases zinc levels, leading to activation of mitochondrial aconitase and conversion of citrate to isocitrate [29, 30]. This reorganization helps initiate the tricarboxylic acid cycle and causes a radical change in the metabolism of PCa cells. Consequently, tumor cells may be able to obtain more energy in the form of ATP molecules through cellular respiration with aerobic glycolysis or, more commonly observed, use citrate conversion for *de novo* acetyl coenzyme A and fatty acid synthesis [31]. These are unique characteristics of PCa that distinguish it from many tumors. The Warburg effect is excluded due to high oxidative capacity and glucose independence [29, 32]. Zinc plays one of the most important roles in malignant prostate cell transformation. In addition to changing the energy processes, this element determines the proliferative and invasive activity of PCa [33]. Concurrent decreased zinc and citrate levels are associated with PCa progression and metastasis [30, 34]. In PCa, a decrease in spermine secreted by the organ is also observed, and some studies suggest that this is associated with cancer aggressiveness [35].

Over the past decade, the number of studies investigating the metabolic profile of PCa using various platforms has increased significantly [10, 22, 23, 31, 36, 37]. Most studies have identified metabolites characteristic of PCa, including sarcosine and choline in plasma and urine as the most important ones [38]. A. Franko et al. [39] described compounds present in the PCa metabolome, including argininosuccinate, arginine, and proline. These substances are products of the urea cycle, and they were significantly increased in PCa compared to BPH [39]. Another study demonstrated an association between elevated fumarate levels (because of activation of the oncogenic HIF1α and NF-κB pathways) and poor survival in PCa. An association has been found between elevated plasma levels of sphingolipids and caveolin1 and high clinical aggressiveness of PCa [40]. Caveolin1 modifies fatty acid metabolism by activating the conversion of sphingomyelins to ceramide derivatives. These processes increase energy resources in cells and enhance the neoplastic activity.

Some studies have focused on the metabolism of sarcosine and its relationship to PCa. A. Sreekumar et al. provided one of the first important studies of this compound [41]. Liquid and gas chromatography and mass spectrometry were used for metabolic profiling of samples from PCa patients and healthy controls. Uracil, kynurenine, glycerol3-phosphate, leucine, and proline levels were slightly elevated in serum, urine, and prostate tissue of PCa patients. Sarcosine levels were significantly elevated in metastatic PCa compared to controls, as well as in locally advanced PCa compared to BPH [41]. Many subsequent studies have not provided conclusive evidence of an association between high levels of sarcosine in metabolic profiling and the presence of PCa F. Jentzmik et al. [42] found no association between sarcosine concentration and the presence of a malignant process in the prostate when stratified by Gleason score. Some other studies show conflicting results [43, 44]. M. Yousefi et al. [45] measured sarcosine levels in 67 patients, including 25 healthy patients (control group), 23 with established BPH, and 19 with PCa. A significant increase in serum and urine sarcosine levels was reported in the PCa group. The BPH group had lower levels and the lowest levels were found in the control group [45]. This uncertainty and inconsistency for a single metabolite indicates the need for further improvements in sample preparation techniques, instrumentation, and data analysis methods. A lot of studies are currently underway to identify patterns of metabolic changes in PCa and to determine the “typical” PCa metabolome, and this will undoubtedly contribute to the development of new diagnostic and therapeutic approaches.

PROSPECTS FOR INTEGRATION OF METABOLIC PROFILING IN THE DIAGNOSIS AND TREATMENT OF PCA

In comparison to other -omics, metabolomics is unique in its ability to reflect dynamic changes in organism parameters that lead to a specific phenotype. Metabolomic research can not only identify biomarkers of PCa, but also metabolically differentiate clinical phenotypes

with subsequent patient stratification to determine diagnostic and treatment approaches. Metabolic imaging of PCa has become possible with advances in understanding the abnormal metabolism of prostate tumor cells. Due to the lack of dependence on glucose and glycolysis, PCa cells have low avidity for fluorodeoxyglucose (FDG), which is used in ^{18}F-FDG positron emission tomography/computed tomography [46]. Metabolic profiling can also be used to examine the metabolome of the core biopsy of the removed prostate following radical prostatectomy to stratify patients into risk groups or to predict treatment outcomes. The identification of PCa biomarkers will clearly be one of the most vital clinical applications of metabolomics. Despite the conflicting results of studies on the reliability of sarcosine levels for the PCa detection, other amino acids and their derivatives are currently being investigated as potential markers for malignant processes in the prostate [47, 48]. Identification of PCa risk factors is another application of metabolomics. The development and progression of a tumor is associated with oncogenic mutations in the genetic material of the cell caused by exogenous and endogenous factors. Damaged deoxyribonucleic acid causes metabolic changes. Each factor of genetic damage is characterized by corresponding metabolic rearrangements which are caused both by the production of abnormal amino acids and proteins and by epigenetic changes in the regulation of polypeptide synthesis [36]. Identifying risk factors and specific metabolic profiles associated with them will allow us to establish groups of patients at risk of PCa. Metabolomics can also be integrated into the development of drugs that affect the metabolism of PCa. By targeting key molecules involved in carcinogenesis and metastasis, it will be possible to destroy the pool of malignant cells at an early stage [49, 50].

CONCLUSION

Implementing metabolomics in clinical practice opens new opportunities for diagnosing and treating malignant neoplasms. PCa is one of the most pressing issues in modern oncology and urology, and investigating PCa metabolism broadens our understanding of the neoplastic transformation of healthy prostate cells. The characteristic molecular regulation of intracellular processes makes PCa a metabolically unique disease that lacks the "classic" features of biochemical atypia seen in most solid neoplasms. By understanding the PCa metabolome, we can discover new biomarkers of the disease, improve early-stage diagnosis, and contribute to the development of new targeted drugs. The number of metabolomic studies of PCa is currently growing, and new mechanisms of carcinogenesis are being revealed. The active use and development of metabolomics along with other -omics will transform the management of PCa patients.

ADDITIONAL INFORMATION

Authors' contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study. Personal contribution of each author: V.N. Pavlov, M.F. Urmantsev, M.R. Bakeev — data analysis, writing the text of the manuscript.

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