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Metabolomics-Based Stratification of Cancer Subtypes and Treatment

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ABSTRACT

Metabolomics, the comprehensive study of small molecules within biological systems, has emerged as a pivotal approach in cancer research, offering deep insights into tumor biology. This paper explores the role of metabolomics in the stratification of cancer subtypes and its implications for personalized treatment. The paper explored the biological basis of metabolomics in cancer, focusing on how metabolic alterations reflect the underlying molecular characteristics of different tumor subtypes. Various techniques, such as nuclear magnetic resonance (NMR), liquid chromatography (LC), and mass spectrometry (MS), are examined for their effectiveness in identifying metabolic biomarkers specific to certain cancer subtypes, particularly breast and lung cancers. Case studies highlight the potential of metabolomics to guide precision medicine by identifying subtype-specific metabolic fingerprints, which could revolutionize cancer diagnosis, prognosis, and treatment strategies. The integration of metabolomics into clinical oncology holds promise for the development of more targeted and effective therapies, ultimately improving patient outcomes.

Keywords: Metabolomics, Cancer Subtypes, Precision Medicine, Biomarkers, Tumor Metabolism.

INTRODUCTION

Metabolomics is defined as the study of the metabolome: the collection of small molecules, such as amino acids, lipids, organic acids, and sugars within an organism or biological system, and could be considered as the ultimate layer of regulation within a cell, reflecting the existing state of operation and its chemical aspects [1]. Metabolomics can be defined as the large-scale study of metabolites in any biological organism. This technology is. Used for the detection and quantification of low-molecular-mass metabolites, typically below 1,500 Da. Metabolomics detected metabolites play a critical role in severe illnesses, ranging from metabolic disorders, central nervous system dysfunctions, mitochondrial diseases to more common and life threatening diseases such as cancers [2, 3]. Cancer is characterized by uncontrolled cell growth. Metabolomics offers a novel way of characterizing the two states of normal and cancerous cells [4]. The fact that tumor cells develop and grow in a microenvironment with different characteristics from those of normal tissues suggests that a phenotypic plasticity could arise in these cell states, impacting their molecular and metabolic profiles. Understanding the biology of cancer from a metabolomics perspective would provide novel insights for the study of tumor initiation, formation, and progression, including the basic concepts of energy metabolism adaptation of tumor cells, metabolic dependencies between mutant oncogenes and the development of the tumor phenotype, as well as implications for personalized therapy [5].

BIOLOGICAL BASIS OF METABOLOMICS IN CANCER STRATIFICATION

The biochemical transformation processes underlying energy production and biosynthetic processes have been recognized as a hallmark of the cancer cell [6]. The metabolic state of the cell is determined by both the genotype (genetic mutations) and epigenotype (DNA methylation, non-coding RNA genes, histones and their modifications), determining the amount and the activity of each protein in the cell [7]. At the

cellular level, mutations affecting the expression and/or activity of metabolic enzymes cause biochemical alterations affecting specific metabolic pathways (e.g., the Warburg effect) [8]. Furthermore, interactions between cells, mediated by both soluble factors and extracellular vesicles, can transmit alterations of the metabolic state to cells in the vicinity (e.g. metabolic cooperation) [9]. At the tissue level, microenvironmental alterations, like hypoxia and deprivation of nutrients, also affect cell metabolism (e.g., glycolytic tumors). At the organism level, there are metabolism-related characteristics of a tumor (e.g., aggressiveness) that correlate with specific alterations of the metastatic niche (e.g., Ca2+ concentration, glycosylation) [10]. Understanding the biochemical or functional metabolic differences between molecular subtypes of a specific tumor type (e.g., the subtype definition of breast cancer) could offer an interesting way to identify new subtype-specific treatment strategies [11, 12]. This goal appears to be particularly relevant for breast cancer because there are 4 different molecular subtypes (luminal A, luminal B, HER2-positive and triple negative) and multiple active clinical studies where specific drugs are tested for each subtype. Significant metabolic alterations in breast cancer have been studied for many years in the literature applying different techniques from nuclear magnetic resonance- (NMR-) based approaches to liquid chromatography (LC), gas chromatography (GC), and mass spectrometry- (MS-) based approaches. Generally speaking, a core of metabolites, namely, glycine, taurine, phosphocholine and lactate, is consistently upregulated in tumor samples with respect to normal samples [11, 12].

METABOLOMICS TECHNIQUES AND TECHNOLOGIES

Breast and lung cancer are two of the most prevalent malignancies in the world. Their early detection via non-invasive means, which are less expensive and would allow population screening, could have a powerful impact on overall survival. Metabolomics, which is the analysis of all low-molecular weight compounds in a biological system, can tackle these issues [13]. A screening metastudy demonstrates the feasibility of lung cancer biomarker studies based on NMR spectroscopy of urine, tissue, and high-throughput cell culture medium samples. Despite the different analytical methods, sample handling, and chemometric approaches employed by several laboratories, there is a core set of metabolites that is common to all studies [14]. The increased level of urinary and/or tissue hippurate, pyridoxate, myo-inositol, formate, succinate, pyruvate, uridine, isocitrate, cadaverine, creatinine, 2-oxoglutarate, and tryptophan-all aromatic or branched-chain amino acids-are all indicative of malignancy [15]. Given the molecular and cellular complexity of cancer and the ongoing discussion about its definition and classification, a systems biology approach using a database of primary human tumors can provide insight into cancer as a unique pathway [16]. In its one-gene/four-pathway expression-based classification schema, breast tumors are grouped into basal, luminal A, luminal B, and ErbB2 subtypes. An exploratory analysis of global metabolomic profiling of matching breast cancer, adjacent normal-tissue, and chronic benign (fibrocystic disease) tissue pairs reveals a distinctively altered metabolomic profile reflecting tumor status and molecular subtypes within the same biological matrix [16, 17, 18].

CASE STUDIES: METABOLOMICS IN STRATIFYING DIFFERENT CANCER TYPES

Tumor metabolism is an emerging field of cancer research, arising from the acknowledgment that biochemical transformation processes underlying energy production and biosynthetic processes have been recognized as a hallmark of the cancer cell. Identification of metabolic differences between molecular subtypes of breast tumors has been proposed as a way to identify new subtype-specific treatment strategies. Despite many years of intense study, breast cancer metabolism has yet to yield an understanding of metabolic differences between distinct tumor subtype, which could lead to novel therapeutic approaches. Metabolic alterations in breast cancer have been studied for many years using a variety of techniques, including nuclear magnetic resonance (NMR), liquid chromatography (LC), and gas chromatography (GC). All studies report differences between tumor versus nontumor tissues [19, 20, 19]. Metabolomics is a relatively new diagnostic tool, which enables a deep insight into the body metabolism at a cellular level. The overview of the metabolomics methodology is presented. The potential of this approach in diagnosing and stratifying lung and breast cancers is shown. There is opportunity to identify a set of metabolites, which is specific for a certain metabolic status (the metabolic fingerprint). Changes in the metabolome precede not only clinical symptoms but also other laboratory findings (this concern not only a cancer disease). Therefore, if sufficiently validated, this approach seems to be very promising especially in screening and early diagnosing [21, 22, 23].

METABOLOMICS-GUIDED PRECISION MEDICINE IN CANCER TREATMENT

Precision medicine is a revolutionary paradigm that aims to tailor the best therapeutic intervention possible to each individual patient by associating their clinical and biological characteristics with the

probability of response to treatment. It thrives on the abundance of 'big data': clinical, omics-based, or environmental, often captured long before the therapeutic decision is made. Biochemical information regarding metabolites in biological fluids (serum/plasma, urine, tissues) is uniquely well positioned on the precision medicine stage since the metabolome can be influenced by numerous factors including genetics, microenvironment, pathology, therapy, etc. The pressure of accumulating evidence: correlations between altered cancer metabolism and specific cancer hallmarks; the dynamics of metabolites as functional messengers encompassing information regarding their source, fate, and influence on cellular behavior, make cancer metabolomics an attractive diagnosco-therapeutic tool for understanding biological responses to stimuli, including treatment [24, 25, 26]. A metabolic fingerprint exposed to and/or obtained from a specific physiological condition can be a referent mode indicating current health status. By identifying the patterns of metabolites accounting for the metabolic fingerprint of normal physiology, disease-induced perturbations can be detected. However, it must be noted that technical aspects of the experiment (analytical techniques, sample handling, pre-analysis, blank, and normalization issues), as well as biological assemblages (biological matrices, sample population, intra- and inter-group homogeneity) have a crucial influence on the quality and reliability of the results obtained [27, 28].

CONCLUSION

Metabolomics has the potential to revolutionize cancer diagnosis and treatment by providing a detailed understanding of the metabolic alterations associated with different cancer subtypes. By identifying unique metabolic fingerprints, this approach offers new opportunities for the stratification of cancer patients and the development of personalized therapies. While challenges remain in standardizing methodologies and validating biomarkers, the integration of metabolomics into clinical practice could lead to significant advances in precision oncology, ultimately improving patient outcomes and reducing the burden of cancer worldwide.

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