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Review article

Short overview on metabolomics approach to study pathophysiology of oxidative stress in cancer

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ABSTRACT

Association of oxidative stress with carcinogenesis is well known, but not understood well, as is pathophysiology of oxidative stress generated during different types of anti-cancer treatments. Moreover, recent findings indicate that cancer associated lipid peroxidation might eventually help defending adjacent nonmalignant cells from cancer invasion. Therefore, untargeted metabolomics studies designed for advanced translational and clinical studies are needed to understand the existing paradoxes in oncology, including those related to controversial usage of antioxidants aiming to prevent or treat cancer. In this short review we have tried to put emphasis on the importance of pathophysiology of oxidative stress and lipid peroxidation in cancer development in relation to metabolic adaptation of particular types of cancer allowing us to conclude that adaptation to oxidative stress is one of the main driving forces of cancer pathophysiology. With the help of metabolomics many novel findings are being achieved thus encouraging further scientific breakthroughs. Combined with targeted qualitative and quantitative methods, especially immunochemistry, further research might reveal bio-signatures of individual patients and respective malignant diseases, leading to individualized treatment approach, according to the concepts of modern integrative medicine.

1. Introduction

More than hundred types of malignant neoplasms affect humans and are commonly denoted as cancer. Although very different in place of origin and etiology they all share several common traits recognized today as the hallmarks of cancer [1]. These have been relatively well understood, suggesting pathophysiological association of oxidative stress with carcinogenesis [2]. Yet, even today, cancer patients largely depend on unspecific and often insufficient treatments, chemotherapy and radiation, utilized decades ago, which are often generating oxidative stress, too [3]. This paradox is further stressed by findings of carcinogenic as well as of selectively cytotoxic anti-cancer effects of products of lipid peroxidation, in particular of 4-hydroxnyonenal (HNE) [4]. These, mostly recent, important findings request advanced translational and clinical studies to understand the existing paradoxes in oncology, especially those related to the controversial use of antioxidants tending to prevent or even to treat cancer interfering with the complex mechanisms of the endogenous antioxidant mechanisms, which different between nonmalignant and cancer cells [2,5].

Aiming to improve biomedical understanding of systemic metabolic changes caused by carcinogenesis and by anti-cancer treatments metabolomics uses powerful tools in cancer research, diagnosis and therapy. It goes hand in hand with other –omics, together giving a more comprehensive picture. The ultimate goal of cancer research is finding reliable and specific biomarkers for early detection of cancer cells giving better survival prognosis for patients, along with finding specific metabolic targets for cancer therapies or providing insights into the mechanism of action of drugs used for anti-cancer treatments. Although

Abbreviations: HNE, 4-hydroxynonenal; NMR, nuclear magnetic resonance; MS, mass spectrometry; LC-MS, liquid chromatography-mass spectrometry; GC-MS, gas chromatography-mass spectrometry; CE-MS, capillary electrophoresis-mass spectrometry; MALDI-IMS, matrix-assisted laser desorption ionization imaging mass spectrometry; SIMS, secondary-ion mass spectrometry; DESI, desorption electrospray ionization; NIMS, nanostructure-initiator mass spectrometry; HMDB, Human Metabolome Database; KEGG, Kyoto Encyclopedia of Genes and Genomes; ROS, reactive oxygen species; NADPH, nicotinamide adenine dinucleotide phosphate; GSH, glutathione; PPP, pentose phosphate pathway; Cys, cysteine; Gly, glycine; Glu, glutamate; GPx, glutathione peroxidase; GSSG, glutathione disulfide; CSSG, cysteine-glutathione disulfide; FH, fumarate hydratase; G6P, glucose 6-phosphate; OPA, ophthalmic acid; 2AB, 2-aminobutyric acid; MOC, metastatic tumors originating from primary ovarian cancer; EOC, primary epithelial ovarian cancer; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; LC, liver cirrhosis; GCS, γ-glutamyl-cysteine-synthetase; GS, glutathione synthetase; ESCC, esophageal squamous cell carcinoma; Kyn, Kynurenine

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metabolomics already gave numerous valuable information about carcinogenesis, its applications in cancer research and clinical practice still remain elusive.

In metabolomics research many challenges exist tending to support modern concepts of personalized and integrative medicine. One of the major challenges is the sheer number of metabolites to be reckoned with, which is in particular difficult in case of advanced cancer due to its overall heterogenic nature [6]. Namely, although it is generally assumed that each tumor originates from a single malignantly transformed cell, with each cell division tumor cells progress forming neoplastic mass of mutually heterogenic cells with increasingly higher mutagenic potential. Ultimately, they give birth to cancerous cells with devastating metastatic phenotype and complex metabolic changes that might differ among malignant cells of the same tumor [1]. Further obstacles are found in xenometabolite interferences, sample collection, sample preparation, specificity and sensitivity of the current machines and methods utilized, while also tackling incomplete databases and system networks for easy identification of metabolites and metabolic pathways.

2. Metabolomics approach

2.1. The power of metabolomics

The 'omics' technologies (genomics, transcriptomics, proteomics, and metabolomics) have already impacted considerably the life sciences and yield important insights to advance our understanding of the pathophysiology of common complex diseases like e.g., diabetes [7,8], cardiovascular disease [9], asthma [10], Alzheimer [11] and cancer [12], among others. Each of the 'omics' is important for studies of complex biological systems and pathophysiological processes, complementing each other and the findings provided by the other, more targeted methods, especially by immunochemistry. However, metabolomics, as a downstream endpoint of all biological processes represents a core tool for a global assessment of metabolites within a biological system and reveals a specific 'snapshot' of the metabolic fingerprints under particular cellular processes that is closely related to the phenotype [13]. The metabolome consists of a complex mixture of thousands of metabolites, small-molecular-weight intermediates (typically with the molecular mass of 80–1500 Da), from a variety of metabolite classes including sugars, amino acids, oligopeptides, lipids, organic acids etc. The wide chemical diversity is further complicated by interferences of endogenous metabolome with the exogenous, i.e. with chemicals originating from environmental contaminants, drugs, additives, toxins and other xenobiotics [14–16]. Moreover, the size of the human metabolome is still being under estimation and might even exceed 100.000 molecules or more if we consider all intermediates and secondary metabolites [15]. In this countenance metabolomics is investigating complex biochemical interactions among different metabolites (metabolome) but is also building a global network to provide unique insight into metabolic reactions underlying activities of the proteins/peptides and gene expression in respect to the other bioactive molecules, including those important for the onset and control of oxidative stress and lipid peroxidation, as is the glutathione (GSH) system (Fig. 1).

3. State-of-the-art technologies in metabolomics

The development of robust, high-throughput metabolomic platforms, predominantly based on nuclear magnetic resonance (NMR) and mass spectrometry (MS) greatly facilitate metabolomics to address clinical questions as therapy and diet selection, treatment efficiency estimation, monitoring and eventually discovering novel biomarkers [16]. Due to the high complexity, compositional diversity of physicochemical properties and concentration magnitude, one of the major analytical challenges in metabolomics is to generate a representative coverage of the studied metabolome. Particularly the untargeted MS based multiplatform approaches, characterized by high sensitivity and reproducibility such as direct infusion MS (DIMS), liquid chromatography (LC-MS), gas chromatography (GC-MS) or capillary electrophoresis (CE-MS) significantly advances evaluating a complete set of metabolites [16,17]. The LC-MS is capable of detecting the widest range of metabolites, both small and large, polar and non-polar molecules, so the resulting data contain thousands of 'metabolic features', where each represents a unique mass-to-charge ratio in a given retention time value. Relatively easy sample preparation is undoubtedly an advantage, too. On the other hand, GC-MS with its strengths of high reproducibility, separation and easy metabolite identification pave the way for detection of small, volatile compounds (e.g., sugars, free fatty acids, organic acids, amino acids or Krebs cycle metabolites), although the technique has its limitations as sample derivatization is required. Additionally, CE-MS platform associated with high resolution offers a complementary approach for analysing polar or ionic compounds in complex aqueous matrices. Apparently, a limitation of LC-MS, GC-MS and CE-MS methods is the loss of spatial information that results upon metabolite extraction from the samples. Therefore, advanced molecular imaging approaches of metabolomics, such as MS-based matrix-assisted laser desorption ionization (MALDI-IMS) [18], secondary ion MS (SIMS) [19], desorption electrospray ionization (DESI) [20] or nanostructure-initiator mass spectrometry (NIMS) [21] can be an important alternative that provides positional information on the distribution of endogenous metabolites as well as for detection of administrated pharmaceuticals within tissues, thus offering a powerful tool to explore and monitor the effects of e.g. cancer metabolic reprogramming.

4. Metabolomics workflow

All metabolomics studies follow a common methodological pipeline from experimental design, sample collection and metabolite extraction, through data collection and analysis to biological interpretation [16,22]. To ensure a highest quality level of thus generated data, exceptional caution should be taken in each step of the workflow. In case of cancer related studies, where apart of blood plasma/serum or urine samples it is common to analyse tumor tissue, particular attention should be given to the sample harvesting and metabolite extraction. Tissues are complex structures composed of heterogeneous mixtures of morphologically and functionally distinct cell types, which is in case of cancer further complicated by the differences in cancer cell viability and inflammatory response to cancer growth and decay. Therefore, collection of representative and homogenous tissue sample requires critical evaluation which is challenging in general, but even more difficult in case of cancer samples which might comprise well-oxygenated regions around the growing rim, whereas the other, central regions might be necrotic [23]. For the tissue analysis it is also important to remove residual blood before storage to avoid the contamination coming from blood metabolome. Additionally, the ongoing biochemical reactions that could modify the metabolic content and provoke ex vivo alteration of sample composition should be stopped as soon as possible following sample harvesting (metabolism quenching) [23]. Such factors among many others may result in increased biological variability, which should be taken into account during data treatment and interpretation of thus obtained results.

5. Oxygen metabolism and redox balance

Aerobic organisms have evolved towards oxygen consumption to gain more efficient production of energy. In higher organisms oxygen is also involved in immunological responses, detoxification of xenobiotics, inflammation and neurotransmitter catabolism [24]. One of the consequences of oxygen metabolism is also production of reactive oxygen species (ROS), which are short-lived and very reactive, so they can react with all biological molecules, changing their structure and function.

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