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REVIEW ARTICLE

Metabolomics Applications in Precision Medicine: An Oncological Perspective

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Abstract: Nowadays, cancer therapy remains limited by the conventional one-size-fits-all approach. In this context, treatment decisions are based on the clinical stage of disease but fail to ascertain the individual´s underlying biology and its role in driving malignancy. The identification of better therapies for cancer treatment is thus limited by the lack of sufficient data regarding the characterization of specific biochemical signatures associated with each particular cancer patient or group of patients. Metabolomics approaches promise a better understanding of cancer, a disease characterized by significant alterations in bioenergetic metabolism, by identifying changes in the pattern of metabolite expression in addition to changes in the concentration of individual metabolites as well as alterations in biochemical pathways. These approaches hold the potential of identifying novel biomarkers with different clinical applications, including the development of more specific diagnostic methods based on the characterization of metabolic subtypes, the monitoring of currently used cancer therapeutics to evaluate the response and the prognostic outcome with a given therapy, and the evaluation of the mechanisms involved in disease relapse and drug resistance. This review discusses metabolomics applications in different oncological processes underlining the potential of this omics approach to further advance the implementation of precision medicine in the oncology area.

Keywords: Precision medicine, Metabolomics, Oncology, Biomarker, NMR, PLS-DA.

1. INTRODUCTION

Precision medicine promises to tailor therapies for each individual by delivering more effective drug treatments while avoiding or reducing adverse drug reactions. Towards this end, considerable efforts have been made over the last few years in the field of pharmacogenomics, with a focus on genotyping and identifying specific genetic variations associated with drug response. However, clinical pharmacology would benefit from the introduction of new methodologies capable of providing information that could complement this genomic information [1]. This is necessary because drug metabolism and utilization involve many different enzymes, multiple organs, several compartments and even the microbiome, and are not always possible to screen for all possible genetic or tissue variants. Furthermore, because drug metabolism varies with ethnicity, age, gender, weight, height, and diet – as well as other environmental and physiological variables – it can be particularly challenging to predict how an individual will respond to a drug based on their genotype alone [1-2].

In this context, the possibility to directly evaluate the phenotype of individuals will play a significant role in determining the appropriate drug treatment or in predicting the response to therapeutic interventions. Metabolites represent the end products of biochemical processes, and their concentrations are extremely sensitive to genetic and environmental changes. Similar to the terms "transcriptome" or "proteome," the set of metabolites synthesized by a biological system constitutes its "metabolome" [3]. The close association between the metabolome and the genotype of an individual also extends to its physiology and surrounding environment, thus offering metabolomics an opportunity to assess genotype-genotype and genotype-environment interactions [4]. Metabolomics is closely linked to the overall physiopathological status of an individual. Thus, metabolomics may incorporate the biochemical events of thousands of small molecules in the cells, tissues, organs, or biological fluids. The qualitative and quantitative alteration of the metabolite composition as a consequence of pathological processes or drug administration translates into complex metabolic signatures [5]. The analysis of these signatures can potentially provide useful information for the diagnosis and prognosis of patients as well as for predicting pharmacological responses to specific interventions. Furthermore, specific metabolic signatures occur after drug treatment, thus providing information from pathways targeted or affected by drug therapy.

Nowadays, tumor genomic profiling is routinely used to classify tumor types, identify driver or germline mutations,

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perform prognostic assessments and make therapeutic decisions [6, 7]. However, the heterogeneity of cancer genomes and cancer tissues can make it difficult to determine the underlying causes or ascertain the optimal treatment. Furthermore, the elevated number of mutations and multiple combinations of tumor suppressors and oncogenes make individualized tumor classification or customized therapy almost impossible [8]. In general, multiple biochemical pathways are affected, owing to the fact that as cancer progresses, multiple defects in biochemical pathways arise as cancer subverts normal metabolism in an effort to survive [9]. Furthermore, metabolic requirements of cancer cells are different from those of most normal differentiated cells, exhibiting different metabolic phenotypes [10, 11]. Some tumors seem to prefer aerobic glycolysis (Warburg effect) [12], others depend more on glutaminolysis [13], and others still are dependent on one-carbon metabolism (choline or folate) [14]. Certain tumors may use a combination of two or more of these metabolic pathways [10, 11, 13]. Using metabolomics to identify the specific metabolic subtype of a particular tumor would enable better customization or informed adjustment of cancer therapies [15].

In this review, we provide specific examples of metabolomics applications in the field of clinical pharmacology and precision medicine with a focus on the therapeutic management of cancer (Fig. **1**).

2. MOLECULAR SUBGROUPS BASED ON METABOLIC SUBTYPES

Oncological processes share a common phenotype of uncontrolled cell proliferation. However, there are also disease-specific alterations in metabolism associated with the metabolic reprogramming taking place during neoplastic transformation [16-20]. Similar to the wide variety of genomic alterations exhibited by tumors, metabolic transformation observed in neoplastic processes is also heterogeneous and extremely sensitive to tissue type, proliferation rate, *etc.* [21, 22]. Metabolic phenotyping aims to obtain a comprehensive analysis of biological fluids or tissue samples. This analysis allows biochemical classification of a person´s physiological or pathological state and can be extremely useful in patient stratification. So far, patient stratification has been mostly performed according to genetic variants, and there are an increasing number of examples demonstrating how genetics can improve the selection of therapies for particular patient classes [23-29]. In this context, the identification of distinct metabolic reprogramming events or metabolic subtypes in cancer patients can potentially inform clinicians on factors that will enhance diagnosis, prognosis or the choice of therapy [30]. The characterization of specific metabolic alterations associated with different neoplastic processes has been the subject of different studies in recent years.

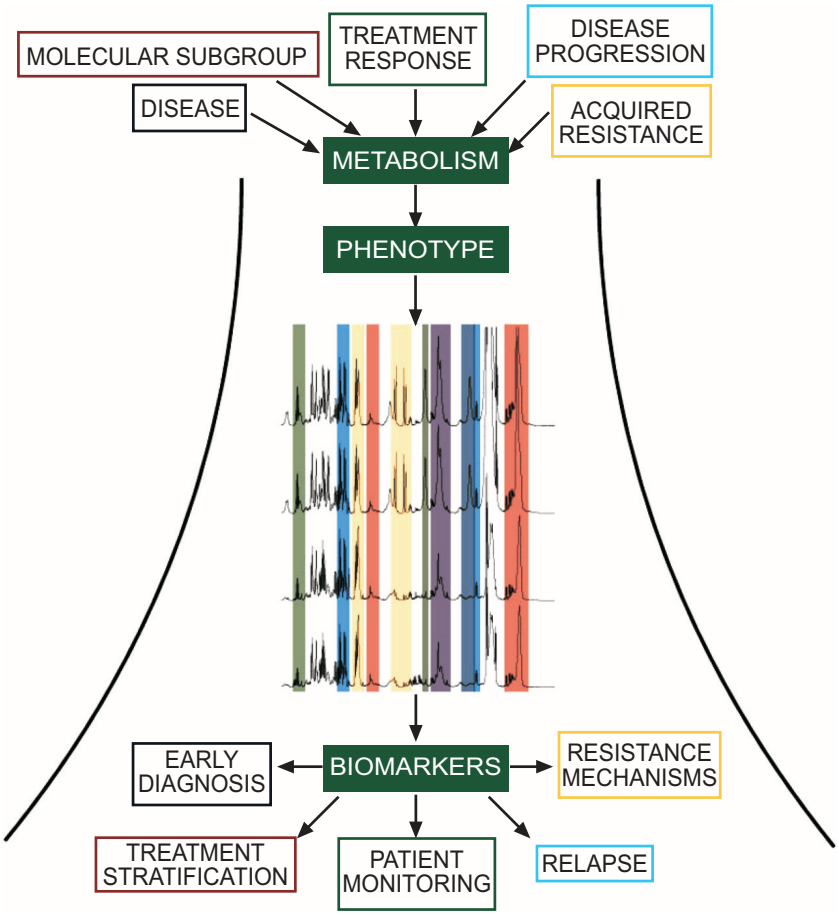

Fig. (1). Schematic diagram summarizing the impact of different pathological and pharmacological processes in the metabolism and its application to the identification of clinical biomarkers for precision medicine.

Chronic lymphocytic leukemia (CLL) is a disease that exhibits heterogeneous clinical behavior, with patient survival times ranging from months to decades [31-32]. Treatment course for this disease has been traditionally based on staging systems [33, 34] enabling the classification of patients into specific outcome groups. Unfortunately, none of those systems facilitate the early stage diagnosis or the discrimination of stable and progressive forms of this disease [35]. In this context, although several omics approaches have been shown to identify differences in CLL patient groups [36-38], they are somewhat limited due to their lack of correlation with the dynamic nature of biochemical function [39]. MacIntyre *et al.* [40] performed a Nuclear Magnetic Resonance (NMR) based metabolomics study to examine serum metabolomic profiles of early stage, untreated CLL patients classified on the basis of the mutational status of the immunoglobulin heavy chain variable region (IGHV) or on the expression level of ZAP70; two approaches routinely used in the clinical management of CLL patients. Metabolic profiles of CLL patients exhibited higher concentrations of pyruvate and glutamate and decreased concentrations of isoleucine compared with controls. Differences in metabolic profiles between unmutated (UM-IGHV) and mutated IGHV (M-IGHV) patients were determined using partial least squares discriminatory analysis (PLS-DA). UM-IGHV patients had increased concentrations of lactate, fumarate, cholesterol and uridine. Furthermore, their metabolic profiles were characterized by decreased concentrations of pyridoxine, glycerol, 3-hydroxybutyrate and methionine. PLS-DA models based on the expression level of ZAP70 showed poor goodness-of-fit values when compared with the classification based on the IGHV mutational status, thus indicating that the latter correlates better with the metabolic profiles associated with the disease. The results highlighted the usefulness of metabolomics as a non-invasive tool for discriminating different CLL molecular subgroups.

Pancreatic cancer is one of the leading causes of death from cancer throughout the world and its 5-year survival rate is less than 5%. Pancreatic ductal adenocarcinoma (PDAC), the most common type of pancreatic cancer, is the most lethal cancer because it is usually diagnosed at an advance stage and is resistant to therapy [41, 42]. Surgery remains the only curative option, although less than 20% of PDAC patients are suitable for surgical resection. Even after complete resection, there is still a significant subpopulation at risk of rapid deterioration and metastatic relapse [43, 44]. One reason for poor outcomes in PDAC may stem from the lack of effective pretreatment evaluation methods to select an optimal therapeutic strategy for an individual patient. Using metabolomics approaches, Daemen *et al.* [45] identified three highly distinct metabolic subtypes in PDAC characterized by different proliferative capacities. Two of them, the glycolytic and lipogenic subtypes, exhibited remarkable differences in the utilization of key metabolites associated with energy metabolism (glucose, glutamine), as well as mitochondrial function. The lipid subtype found in primary PDAC tumor samples showed a strong association with an epithelial phenotype, and the glycolytic subtype with a mesenchymal phenotype, thus indicating functional relevance in the progression of the disease. Based on these findings, the authors proposed a model in which both tumor subtypes are metabolically structured to preferentially use different metabolites for producing tricarboxylic acid (TCA) intermediates and de novo lipogenesis. Furthermore, their analysis suggests that mesenchymal tumors may be more vulnerable to ROS-inducing agents, potentially through differences in NADPH balance and antioxidant responses [46]. Taken together, the results provide valuable predictive utility and thereby provide clinical evaluation of a variety of metabolic inhibitors such as monocarboxylate transporter 1 (MCT1) and glutaminase inhibitors currently undergoing phase I testing across a variety of tumor indications.

Another example of the application of metabolomics approaches for characterizing molecular subtypes is provided by the work of Fan *et al.* [47] on breast cancer (BC). This neoplastic process is the most common cause of death among women worldwide [48]. Human epidermal growth factor receptor 2 (HER2) and estrogen receptor (ER) are the two key molecular biomarkers to segregate the most distinct biological subgroups of BC [49]. Each subtype of BC is accompanied with characteristic molecular features, prognosis and clinical responses to available medical therapies [50]. Determining the molecular subtype of BC is critical for personalized treatment. However, it requires repeated biopsies and subsequent histopathology to study molecular and genetic information from tumor cells for BC diagnosis and subtype classification. This analysis is invasive and time-consuming [51, 52], and it would be desirable to develop rapid and sensitive analysis for discriminating different BC subtypes. In this context, the authors, using ultraperformance liquid chromatography-quadrupole time of flight mass spectrometry (UPLC-Q/TOF-MS) and gas chromatography-quadrupole mass spectrometry (GC-Q/MS), examined the metabolic profiles of healthy women and BC patients. The results of this study revealed that the metabolic profile of HER2-positive patients, compared with HER2-negative patients, is characterized by specific alterations in glycolysis, gluconeogenesis and fatty acid biosynthesis. Moreover, it was found that ER-positive patients, compared with the ER-negative group, exhibited increased metabolism of certain amino acids (*i.e.,* alanine, aspartate, glutamine) and purine, and decreased glycerolipid catabolism. A combination of differentially expressed metabolites (carnitine, lysophosphatidylcholine (16:1, 20:4), proline, alanine, glycochenodeoxycholic acid, valine and 2-octenoic acid) was finally found for the discrimination of BC subtypes. Overall, the findings demonstrate that the analysis of plasma metabolomic profiles provides a test that is faster, less costly, and non-invasive, that could be used in combination with other more invasive screening procedures. Furthermore, the possibility of discriminating different BC subtypes could facilitate the identification of new therapeutic pathways from which novel agents might be developed.

A final example of the metabolomics potential to identify disease-specific molecular fingerprints is the recent study by Zhao *et al.* [53]. Over the last few years, the molecular characterization of gliomas, as opposed to the classical histopathological one, has emerged as a more accurate method to characterize this disease. Several studies have identified alterations in different signaling pathways (phosphoinisitide 3-kinase (PI3K), RTK/RAS/PI3K, EGF receptors (EGFR), p53, retinoblastoma (RB), PTEN) as main drivers for high-

grade gliomas [54, 55]. The understanding of how underlying metabolic alterations could contribute to the aggressive phenotype in tumors [55, 56] has triggered the interest in using metabolomics for characterizing gliomas [57]. Thus, using Grade II to IV glioma tumor tissues, Chinnaiyan *et al.* identified a metabolic classifier that could group glioma tumors into three different subclasses with distinct prognostic relevance [57]. In agreement with these findings, recent studies have underlined the role that specific metabolic alterations can play in the progression of gliomas. Thus, it has been reported that hyperglycaemia is associated with a shortened overall survival of glioma patients [58]. Other studies have suggested that pre-existing diabetes and increased body mass index (BMI) could also represent additional risk factors for the progression of this disease [59]. More recently, Zhao *et al.* have reported a metabolomics study focused on the analysis of plasma samples from glioma patients. The data were tested for correlation with glioma grade (high *vs* low), glioblastoma (GBM) *vs.* malignant gliomas, and isocitrate dehydrogenase (*IDH*) mutation status. They identified a set of 18 metabolites showing significantly different levels between high- and low-grade glioma patients. Similarly, 2 and 6 metabolites significantly differing between GBM and non-GBM, and *IDH* mutation positive and negative patients were also identified. Finally, the results of a pathway analysis revealed that *IDH* mutation positive patients, compared with mutation negative ones, exhibited decreased concentrations of metabolites associated with the creatine pathway, thus perhaps reflecting an increased biochemical activity of this pathway in tumors carrying this mutation. Taken together, the results show that certain metabolites and metabolic pathways could be useful for differentiating glioma tumor phenotypes, thus providing additional support to the molecular classification of gliomas.

3. PREDICTIVE BIOMARKERS: PHARMACOMETABOLOMICS

The identification of biomarkers for therapy selection can optimize treatment of cancer patients and potentially also reduce the cost of prescription drugs for the healthcare system. Biomarker discovery through metabolomics can play a large role in the discovery of metabolic biomarkers, both in cases where other biomarkers are available by providing additional biomarkers to strengthen the predictive accuracy, and also in cases where no therapy response predictive biomarkers are available yet [60]. The application of metabolomics to the prediction of the specific patient response to drug treatments is termed pharmacometabolomics. This approach is based on the identification of individual´s metabolomics profiles, which represent a large repertoire of metabolites reflecting the complex interactions among gene expression, protein expression, physiopathological conditions, age, gut microbiome, and the environment better than other omics profiles [61]. Consequently, the metabolomics profile is more closely associated to a patient´s pharmacological phenotype and could be more informative than genomic or proteomic data when trying to understand the mechanisms of inter-patient variability in response to drug therapy [62-65].

Blackshall *et al.* performed a study focused on the evaluation of the toxicity predictive ability of pretreatment serum metabolic profiles obtained using ^{1}H-NMR spectroscopy in patients with inoperable colorectal cancer (CRC) receiving single agent capecitabine. This compound is an oral prodrug of 5-fluorouracil (5-FU) [66] that is absorbed from the gastrointestinal tract and undergoes a three-step activation process to 5-FU within the tumor [67]. The aim of this study was to determine whether a metabolomic profile obtained from pretreatment serum samples could predict toxicity from capecitabine in patients with advanced CRC. Using serum samples collected from patients with a diagnosis of locally, advanced or metastatic CRC (mCRC), they found that toxicity severity over the treatment period was associated with pre-existing high levels of different low-density lipoprotein-derived lipids. The results of this study suggest that metabolomic profiles can discriminate patient subgroups more prone to adverse events and have a promising role in the evaluation of therapeutic treatments for oncological patients before initiating chemotherapy.

Another study in the area of mCRC was carried out by Bertini *et al.* [68] using ^{1}H-NMR spectroscopy. In this case, they focused on the analysis of serum samples from mCRC patients before third-line treatment with cetuximab and irinotecan, and healthy individuals. The statistical model generated could robustly discriminate healthy individuals from mCRC patients with 100% cross-validated accuracy. General applicability of the resultant classifier was successfully validated using an independent set. The capability of the ^{1}H-NMR profiles to predict overall survival (OS) after start of treatment with cetuximab and irinotecan, using pretreatment serum samples, was tested on a subset of samples from the training set with maximally divergent OS, and the classifier validated on the independent set of patients with mCRC. Results showed that the levels of several metabolites were significantly different between mCRC patients and healthy individuals, as well as between mCRC patients with short and long OS. In particular, it was found that serum metabolomic profile of mCRC is characterized by a higher intensity of the signals of CH_2-COOR of lipids and the N-acetyl resonance of glycoproteins; this effect being larger for patients with short OS. Furthermore, patients with short OS showed decreased serum concentrations of polyunsaturated lipids. Overall, their findings show that ^{1}H-NMR profiling of patient serum samples not only offers a strong metabolomic signature of mCRC but also its analysis can lead to the development of a tool for predicting OS.

As pointed out previously, BC is a clinically heterogeneous disease, which requires a variety of treatments and leads to different outcomes. In this context, the early identification of chemotherapy responder and non-responder patients has critical implications for improving long-term survival, as well as for the identification of other therapeutically effective treatment regimes. In a study carried out by Wei *et al.* [69], serum metabolomic profiles, using a combination of NMR spectroscopy and liquid chromatography-mass spectrometry (LC-MS), were obtained to predict the response to neoadjuvant chemotherapy in BC patients. Samples were collected from BC patients with complete, partial and no response to chemotherapy. Using this experimental approach, it was found that the concentration of four metabolites, three (threonine, isoleucine, glutamine) identified by NMR and one (linolenic acid) using LC-MS were signifi-

cantly different when comparing response to chemotherapy and were well correlated with pathologic complete response (pCR). A predictive model developed combining NMR and MS derived metabolites correctly classified pCR and stable disease (SD) BC patients with 100% specificity and 80% sensitivity. These results indicate that several blood-based metabolites are response predictive and that this approach, although requiring further validation using larger patient cohorts, could result in more precise treatment protocols for BC patients.

A more recent study, focused on a homogeneous population of BC patients, has been reported by Miolo *et al.* [61]. The authors applied a pharmacometabolomics approach to identify biomarkers potentially associated with pCR to trastuzumab-paclitaxel neoadjuvant therapy in HER-2 positive BC patients. Based on histological response, the patients were subdivided into two groups, good and poor responders. The pretreatment serum metabolomic profiles of all patients were analyzed using a targeted approach by LC-MS. Differences in the metabolomic profile between the two groups were investigated by multivariate statistical analysis. The most relevant metabolites in the comparison between the two groups of BC patients were spermidine and tryptophan. Good responders showed higher amounts of spermidine and lower amounts of tryptophan compared with the poor responders. The serum levels of these two metabolites identified patients who achieved complete response with a sensitivity of 90% and a specificity of 87%. The results provide an indication of the impact that the specific patient´s metabolism has in the response achieved following cancer treatment, and could represent a relevant tool for selecting patients more prone to benefit from the trastuzumab-paclitaxel neoadjuvant therapy.

4. TREATMENT MONITORING

For decades, and even in modern medicine, individual metabolites have been used for diagnosis and monitoring of disease progression and therapy response [70-72]. Because of its exceptional ability to cover the metabolome, metabolomics provides a much more comprehensive assessment of patient´s biological/health status than the measurement of single metabolites as has been used in conventional disease management. This makes metabolomics a powerful tool for the identification, quantification and development of biomarkers [70]. Interestingly, metabolic signatures have also been characterized for the specific response to several drugs, and the importance of such signatures is due to the fact that they represent the metabolic changes in pathways that are targeted by or affected by drug treatment [73]. Combined examination of disease metabolic characteristics and treatment response could provide metabolic biomarkers very useful for personalization of therapies. Particularly, the investigation of metabolic changes in different neoplastic processes following drug administration is becoming the subject of different studies in recent years [74].

Multiple Myeloma (MM) remains an incurable disease. New approaches are required for improving survival and for the development of the necessary tools to assess the prognosis of MM patients and their response to therapeutic treatments. Puchades-Carrasco *et al.* performed a ^{1}H-NMR spectroscopy study to characterize the specific metabolic profile of MM patients by conducting a comparative analysis of serum samples from healthy individuals and MM patients [75]. Furthermore, a comparison between the metabolic profiles of MM patients at the time of diagnosis and after achievement of complete remission was conducted. An in-depth analysis of the changes in the levels of the metabolites involved in the discrimination between the different groups revealed three different behaviors. Thus, some metabolites (3-hydroxybutyrate, arginine, acetate, *etc.*) whose levels were different when comparing MM patients at diagnosis and healthy individuals did show the same trend when the comparison was performed between MM patients at diagnosis and after complete remission. This behavior could be indicative of metabolic alterations associated with MM that are not modified after patients achieve complete remission. Interestingly, another group of metabolites (lactate, citrate, *etc.*) was characterized by exhibiting variations when MM patients at diagnosis and after complete remission were compared, but not when that comparison included MM patients at diagnosis and healthy individuals. It could perhaps reflect metabolic alterations caused by MM treatment that are not associated with the response to treatment. Finally, there were other metabolites (cholesterol, lipids, glutamine, lysine, *etc.*) displaying changes in the opposite direction after MM treatment was initiated, suggesting these metabolites could be reflecting the metabolic alterations induced by the treatment in the characteristic profiles of MM patients. Overall, this study suggests that the analysis of metabolic profiles of MM patients provides an opportunity for characterizing metabolites associated with treatment efficacy and response.

Renal Cell Carcinoma (RCC) is one of the most chemoresistant cancers, and treatment of its metastatic form (mRCC) usually relies on therapies based on angiogenesis or mTOR inhibitors. A good understanding of the metabolic impact of these therapeutic treatments is critical to predict the patient response and adjust personalized therapies. Jobard *et al.* carried out a metabolomic investigation of serum samples from patients with mRCC to identify metabolic signatures associated with targeted therapies [76]. To this end, pretreatment and serial on-treatment (2 and 5-6 weeks) samples were obtained from mRCC patients receiving either a bevacizumab and temsirolimus combination (experimental arm A) or a standard treatment: sunitinib (arm B) or interferon-α plus bevacizumab (arm C). Metabolic profiles were obtained using NMR spectroscopy and compared on-treatment or between treatments. Their results revealed a specific metabolomic signature associated with the response to the experimental combination of bevacizumab and temsirolimus, together with the presence of an earlier modification of the metabolism, compared to patients treated with the two standard therapies. Unlike the two standard treatment groups, significant changes in different metabolites (glucose, N-acetylglycoproteins, lipids, lipoproteins (LDL and VLDL)) were identified in the experimental arm. After 2 weeks of therapy, only the lipids showed a high discriminatory power. However, a large number of significant changes in several metabolites were identified in the experimental arm after 5–6 weeks of treatment, some of them showing strong discriminatory power. On-treatment samples were characterized by exhibiting elevated levels of several me-

tabolites (acetoacetate, acetone, glucose, glycerol, alanine, glutamine, glycine, isoleucine, leucine, valine, cholesterol, lipids, LDL, VLDL lipoproteins and N-acetylglycoproteins), and decreased levels of ethanol and lactate when compared with pretreatment samples. Taken together, their findings highlight the potential of metabolomic approaches to study effects associated with the mechanism of action of drugs.

Chronic Myeloid Leukaemia (CML) is a myeloproliferative disorder characterized by the presence of the Philadelphia chromosome originating from the t(9;22) (q34;q11) reciprocal translocation. It includes the fusion gene *BCR-ABL1* encoding the Bcr-Abl protein with constitutive tyrosine kinase activity, thus triggering various intracellular signalling pathways that lead to the malignant transformation of the cell [77, 78]. The majority of CML patients have an optimal response to tyrosine kinase inhibitors (TKIs). During the treatment with TKIs, cytogenetic examination and real-time polymerase chain reaction quantitation of residual leukemic cells with an active *BCR-ABL1* gene are used for the monitoring of CML patients. However, these methods evaluate the early response to TKI treatment at 3, 6, and 12 months from the beginning of the treatment [79]. The majority of treatment failures occurs during the first 2 years of the TKI therapy and are not always detected or predicted using routine monitoring. Therefore, new methods for the improvement of the prognostic assessment of CML patients are clearly needed. Karlikova *et al.* [80] examined the metabolome (plasma, leukocytes) of CML patients at the time of diagnosis and after their treatment with hydroxyurea and subsequent treatment with TKIs (imatinib, dasatinib, nilotinib) in comparison with healthy subjects to identify changes in metabolites induced by the disease and its treatment. The global metabolic profiles obtained by LC-MS were able to discriminate CML patients at diagnosis and those treated with hydroxyurea from CML patients treated with TKIs and healthy individuals. Metabolic differences were mainly associated with changes at the level of glycolisis, the TCA cycle and amino acid metabolism. The results of this study underline the potential of metabolomics as an additional method for the assessment of the treatment response in CML patients after TKIs.

GBMs progress rapidly, making response evaluation using Magnetic Resonance Imaging (MRI) not sufficiently effective considering treatment effects are only observed after several months following treatment. Therefore, additional biomarkers providing reliable information on treatment efficacy at an early stage are required. Mören *et al.* [81] analyzed, using GC-TOF-MS, serum samples from patients with GBM during the initial phase of radiotherapy. The study design included the evaluation of samples obtained from GBM patients just before treatment and after the second and fifth radiation doses. Results were compared in relation to previous data from microdialysis in tumor tissue (*i.e.,* the extracellular compartment) from the same patients. Significant changes in metabolite patterns in serum were observed when comparing samples collected before and after early radiotherapy. A number of amino acids and fatty acids together with myo-inositol, creatinine and urea were among the metabolites that experienced a decrease in concentration during treatment, while citric acid was among the metabolites that increased in concentration. The comparison between the results obtained in serum and in tumor extracellular fluid revealed a common pattern in both compartments, with the exception of glutamine and glutamate, whose levels were decreased in serum after treatment and increased in the tumor extracellular fluid. Overall, the findings show that serum metabolomics could be a valuable tool for assessing early response to radiotherapy in malignant glioma.

5. ACQUIRED RESISTANCE AND RELAPSE

The use of metabolomics for the assessment of treatment effect, as both a predictive measure of efficacy and as pharmacodynamic marker, has been shown previously. However, metabolomics can also provide very valuable information regarding other pharmacological events, such as drug resistance and disease relapse. Cancer cells that do not respond or evade therapy play a critical role in the biochemical mechanisms leading to relapse. Therefore, a better understanding of the metabolic rewiring involved in drug resistance could lead to opportunities for the development of new therapeutic strategies [82]. Cancer is a clonal disease able to generate new subclones with modified traits that are naturally selected based on their capabilities to survive and grow in specific circumstances [83-85]. Therefore, cancer cells able to adapt or resist treatment will be selected under therapeutic pressure, thus leading to relapsing disease, which is usually associated with a poor prognosis [84, 86, 87]. In this context, a deeper insight into the biochemical underpinnings of treatment resistance and cancer progression as provided by metabolomics could lead to the discovery of new therapeutic targets and the achievement of individualized disease management [88].

Different mechanisms have been described as potential contributors to imatinib resistance in CML [89-94]. Additionally, the remodelling of cellular metabolism has been explored as a possible mechanism underlying enhanced cell proliferation and growth in the presence of imatinib [95]. Human CML cell lines with loss of imatinib sensitivity display increased glycolytic rate and phosphocoline levels, metabolic alterations that are considered to sustain cell proliferation in these conditions [96]. Imatinib treatment has also been associated with a significant reduction of the nucleic acid and fatty acid synthesis mediated by the inhibition of the pentose phosphate shunt [97]. Inhibitory effects induced by imatinib can be overcome by a shift from oxidative to non-oxidative pathways, thus facilitating the production of critical biomolecules involved in cell proliferation [98]. In a metabolomic study carried out using ^{1}H-NMR, Dewar *et al.* examined the metabolic profiles of a CML cell line (MyL) and a subline displaying resistance to imatinib (MyL-R) [99]. The authors showed that once cells became resistant to imatinib, this condition was maintained even in the absence of this drug. These cells exhibited a different metabolic phenotype to that of the parental CML cell line, and were characterized by a decreased glycolytic rate, as well as by reduced levels of choline derivatives and taurine, and increased creatinine levels. They also demonstrated that the resistant cells maintained a portion of the creatinine pool as phosphocreatine, which may provide an additional energy reserve allowing cells to escape imatinib-mediated cell death. The results of this study show the potential of metabolomics to provide a better understanding of the contribution of cellular

metabolism to particular disease states, drug responses and alterations in biological conditions.

Ovarian cancer (OC) is responsible for the highest mortality of all cancers of the female reproductive system. OCs are generally sensitive to chemotherapy and often initially respond well to standard primary treatment with cytoreductive surgery and first-line platinum and taxane-based chemotherapy [100]. Even though the presence or development of platinum resistance is a major obstacle in successful OC treatment, platinum therapy is still the principal treatment for recurrent tumors [101]. The development of resistance to platinum has been associated with processes that limit the efficacy of this drug (*e.g.,* reduced drug accumulation, drug inactivation or improved drug efflux) or activate different survival mechanisms (enhanced DNA repair, upregulation of anti-apoptotic genes, *etc.*) [102-103]. While advancements have been made in understanding the molecular deregulation underlying chemoresistance, they have not led to the development of therapeutic solutions able to improve the clinical management of chemoresistant tumors. In this context, new strategies for identifying platinum resistant tumors are very much needed. Poisson *et al.* carried out a study aiming to identify the metabolic alterations that are specifically associated with platinum resistance in OC [104]. To that end, a global metabolic analysis of the A2780 platinum-sensitive and its platinum-resistant derivative C200 OC cell line was performed using UPLC-MS and GC-MS. Functional analysis based on KEGG [105] and IPA (http://www.ingenuity.com/) revealed that the methionine degradation super-pathway and cysteine biosynthesis were the top two canonical pathways affected. The main metabolic networks involved in platinum resistance were associated with energy production, and small molecule and carbohydrate metabolism. An in-depth analysis of the data showed that the most significant alterations were associated with pathways involved in glutathione and polyamine synthesis. Overall, the findings show that the chemoresistant C200 OC cells have distinct metabolic alterations that may contribute to its platinum resistance. This study shows that platinum resistance in OC is characterized by a specific metabolic profile, thus providing an opportunity for the identification and therapeutic treatment of chemoresistant tumors [104].

Despite the favorable response to initial therapy, most OC patients relapse within 18 months [106]. Recurrent OC usually develops chemotherapy resistance and invariable is fatal [107]. Recent metabolomic based studies in OC have been applied to the screening of urine, plasma, and tumor tissue from OC patients and control population [108-113]. These studies focused on the discrimination between healthy and OC patients [108-110], and profiling of malignant and borderline ovarian tumors [109], providing a better understanding of OC pathogenesis and facilitating clinical diagnosis of this disease [110, 111, 114-116]. However, to improve survival rates, new efforts should be devoted to investigate metabolic alterations associated with response to OC treatment and disease relapse. In a recent study, Ke *et al.* [115] performed a metabolomic study by rapid resolution liquid chromatography mass spectrometry (RRLC-MS) including plasma samples from OC patients at the time of diagnosis (primary OC patients) and after cytoreductive surgery (post-operative OC patients), matched controls and matched recurrent OC patients. They found that, compared with primary OC patients, relapsed OC patients showed substantial metabolic alterations. A series of amino acids (l-histidine, l-tryptophan, and l-phenylalanine) and amino acid-related metabolites (kynurenine, 2,3-dihydroxyvaleric acid, glyceric acid, and α-ketoisovaleric acid) were remarkably increased in relapsed OC patients compared with the primary OC patients. Further significant alterations in recurrent OC patients were observed within lipid metabolism, as indicated by significantly increased levels of lysophosphatidylcholines (LPCs), lysophosphatidylethanolamines (LPEs) and fatty acids. Recent studies have also suggested that adverse lipid profile raises prostate cancer (PCa) recurrence risk [117]. Therefore, alterations of these metabolites might serve as specific biomarkers for OC recurrence and possibly as metabolism-based drug targets. This study underlines the potential of metabolomics to identify metabolic changes in response to advanced OC, surgery and recurrence, which could facilitate both understanding and monitoring of OC development and progression.

Another example of the application of metabolomics to the identification of metabolic signatures associated with disease relapse is provided by the work of Tenori *et al.* on early stage BC patients [118]. Following surgical excision of the breast lesion and surgical sampling and/or dissection of axillary nodes, BC patients might be offered loco-regional radiotherapy and/or post-operative (adjuvant) systemic therapy. The rationale behind this approach is that residual micrometastatic disease might be eradicated by chemotherapy. If not eradicated, micrometastases might progress to incurable disseminated BC. In current clinical practice, micrometastatic disease is detectable as circulating tumour cells in the peripheral blood and disseminated tumours cells in the bone marrow. However, not all patients with micrometastases will develop clinically evident macrometastatic disease [119]. Furthermore, factors beyond the presence of micrometastases, such as tumour cell dormancy, host immunity, and the microenvironment, influence the clinical outcome. Therefore, novel prognostic and predictive biomarkers are required to guide the use of systemic therapy in individuals with early BC. In this context, Tenori *et al.* explored, using NMR, whether serum metabolomic profiles could distinguish between early and metastatic BC patients, and predict disease relapse in early stage patients. They found that disease relapse is associated with significantly lower levels of histidine and higher levels of glucose and lipids compared with BC patients with no relapse. Although validation studies are required, the study underlines the potential of metabolomics as a host and tumour-derived prognostic tool, thus providing an avenue for predicting disease relapse in individuals with early stage BC.

CONCLUSION

Cancer is a metabolic disease. Cancer cells are characterized by substantial modifications in different metabolic pathways (glycolysis, TCA cycle, oxidative phosphorylation, *etc.*) as well as in the metabolism of lipids and amino acids [120]. In this context, metabolomics holds great promise for a better understanding of the molecular determinants of cancer, as well as could be extremely useful for advancing in the development of new biomarkers for the diagnosis, prognosis

and treatment of neoplastic processes. In fact, this approach has been used to identify and validate molecular mechanisms involved in carcinogenesis and proliferation, as well as biomarkers of clinical value in the diagnosis/prognosis of different neoplastic processes, and even contribute to the staging of cancers and characterization of treatment efficacy [121]. In this review, we have summarized different examples that have emerged in the last few years demonstrating the potential of metabolomics tools and data in preclinical and clinical development. For example, the ability to subclassify patients could contribute to clinical trial design and increase success in choosing patients for trial inclusion. Furthermore, the possibility of identifying metabolic alterations associated with the presence or the response to particular drugs or drug treatments will undoubtedly contribute to get a deeper insight into the mode-of-action of drugs, as well as on characterizing the metabolic impact on the pharmacokinetics and pharmacodynamics of the therapeutic treatments [1]. Finally, metabolomics approaches are very well suited for uncovering other pharmacological events, such as drug resistance and disease relapse. The information derived from these metabolomic studies could in turn help to identify new therapeutic targets and eventually novel molecularly targeted agents that could further facilitate the implementation of precision medicine in the oncology area.

LIST OF ABBREVIATIONS

5-FU	=	5-Fluorouracil
BC	=	Breast Cancer
BMI	=	Body Mass Index
CLL	=	Chronic Lymphocytic Leukemia
CML	=	Chronic Myeloid Leukemia
CRC	=	Colorectal Cancer
EGFR	=	EGF Receptors
ER	=	Estrogen Receptor
GBM	=	Glioblastoma
GC-Q/MS	=	Gas Chromatography-Quadrupole Mass Spectrometry
HER2	=	Human Epidermal Growth Factor Receptor 2
IDH	=	Isocitrate Dehydrogenase
IGHV	=	Heavy Chain Variable Region
LPCs	=	Lysophosphatidylcholines
LPEs	=	Lysophosphatidylethanolamines
mCRC	=	Metastatic CRC
MCT1	=	Monocarboxylate Transporter 1
M-IGHV	=	Mutated IGHV
MM	=	Multiple Myeloma
mRCC	=	Metastatic RCC
MRI	=	Magnetic Resonance Imaging
NMR	=	Nuclear Magnetic Resonance
OS	=	Overall Survival
PCa	=	Prostate Cancer
pCR	=	Pathologic Complete Response
PDAC	=	Pancreatic Ductal Adenocarcinoma
PI3K	=	Phosphoinositide 3-Kinase
PLS-DA	=	Partial Least Squares Discriminatory Analysis
QM-PDA	=	Mesenchymal
RB	=	Retinoblastoma
RCC	=	Renal Cell Carcinoma
SD	=	Stable Disease
TCA	=	Tricarboxylic Acid
TKIs	=	Tyrosine Kinase Inhibitors
TKIs	=	Tyrosine Kinase Inhibitors
UM-IGHV	=	Unmutated
UPLC-Q/TOF-MS	=	Ultraperformance Liquid Chromatography-quadrupole Time of Flight Mass Spectrometry

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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