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Review Article

Narrative Review on Metabolomics and its extensive Applications in Plant Biotechnology and Oncology

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Abstract

Metabolomics is that the study of metabolomes in cells, biofluids, tissues, or organisms to comprehensively determine and quantify each endogenous and exogenous low-molecular-weight (<1kDa) metabolites in an exceedingly high-throughput biological system. Together with alternative omics disciplines, metabolomics has several applications for health, disease, precision and personalized medication, single cell, epidemiologic population studies, metabolic phenotyping, and metabolome-wide interaction studies, preciseness metabolomics, and integrative omics, biotechnology, and applied science. The scientific study of chemical processes involving metabolites, small molecule substrates, intermediates and cell metabolism products is termed as Metabolomics. In particular, metabolomics is the systematic study of the unique chemical fingerprints that specific cellular processes leave behind the study of their metabolite profiles in small molecules. In this review we had covered that how metabolomics is being applied in plant biotechnology and in oncology and how its role had helped the research platform in data interpretation.

Keywords: Biofluids, Cellular, Epidemiologic, Metabolomics, Metabolites.

Introduction

The metabolome represents a complete collection of metabolites that are the end products of cellular processes in a biological cell, tissue, organ or organism (Jordan et al., 2009). The collection of gene products generated in the cell are revealed by messenger RNA (mRNA), gene expression data and proteomic analyses, data that represents one aspect of cell function. In comparison, metabolic profiling can offer an instantaneous snapshot of the cell's physiology (Villate et al., 2021) thus, metabolomics offers a clear functional data of the physiological state (Hollywood et at., 2006). In biological sciences, integrating genomics, transcriptomic, proteomic, and metabolomic knowledge to provide a deeper understanding of cellular biology is one of the challenges of systems biology and functional genomics.

Metabolome and its Role

The metabolome refers to the complete set of small-molecule of <1.5 kDa (Wishart et al., 2007) Within a biological sample, such as a single organism, metabolites such as metabolic intermediates, hormones and other signaling molecules, and secondary metabolites may be identified (Griffin & Vidal-Puig, 2008). In analogy with transcriptomics and proteomics, the term was coined; the metabolome is dynamic, like the transcriptome and the proteome, evolving from second to second. While it is sufficiently simple to identify the metabolome, it is currently not possible to examine the whole range of metabolites using a single analytical process.

Each cell and tissue type has a unique metabolic 'fingerprint' that can elucidate information specific to the organ or tissue. Bio-specimens used for metabolomics analysis include plasma, serum, urine, saliva, faeces, muscle, sweat, exhaled air, and gastrointestinal fluid, but not limited to them (Ulaszewska et al., 2018). The ease of selection enables high temporal resolution, and the host as a whole can be defined because they are still in dynamic equilibrium with the body (Nicholson & Wilson, 2003). Genome can tell what could happen, transcriptome can tell what seems to happen, proteome can tell what makes it happen, and metabolome can tell what has happened and what's going on. Probably the most comprehensive public metabolomic spectral database to date is the Human Metabolome Database (HMDB) (Pearson, 2007). More than 40,000 separate metabolite entries are stored in the HMDB. As stated in the literature, they catalogued about 2500 metabolites, 1200 drugs and 3500 food components that can be found in the human body (Wishart et al., 2007). This information is far from full, accessible from the Human Metabolome Database (www.hmdb.ca) and based on a review of the information available in the current scientific literature (Dettmer et al., 2006).

Tendency of Metabolites

The substrates, intermediates and products of metabolism are metabolites. A metabolite is generally classified as any molecule less than 1.5 kDa in size in the sense of metabolomics (Wishart et al., 2007). But, depending on the sample and method of detection, there are exceptions to this. In NMR-based metabolomics studies of blood plasma, for example, macromolecules such as lipoproteins and albumin are reliably detected (Nicholson & Wilson, 2003) It is usual to refer to 'main' and 'secondary' metabolites in plant-based metabolomics (Villate et al., 2021). A primary metabolite is involved directly in growth, development, and reproduction. A secondary metabolite is not directly involved, but typically has a significant ecological role in these processes. Examples include antibiotics and pigments (Bentley, 1999) By comparison, metabolites are more generally identified as either endogenous (produced by the host organism) or exogenous in human-based metabolomics (Nordström et al., 2006), (Lin et al., 2020) metabolites of foreign substances such as drugs are referred to as xeno-metabolites (Crockford et al., 2008).

Metabonomics – An Introduction

The quantitative measurement of the dynamic multiparametric metabolic response of living systems to pathophysiological stimuli or genetic modification is known as metabonomics. Jeremy Nicholson at Murdoch University pioneered this technique, and it has been used in toxicology, disease diagnosis and a variety of other fields. Historically, one of the first approaches to extend the scope of systems biology to metabolism studies was the metabonomics method (Nicholson et al., 1999), (Nicholson et al., 2002), (Holmes et al., 2008). There was some conflict between metabolomics and metabonomics about the precise distinctions. Although metabonomics is more correlated with NMR spectroscopy and metabolomics with mass spectrometry-based approaches, the difference in the two terms is not related to the choice of analytical platform: this is simply due to uses among different groups that have popularized the various terminology. While there is still no absolute agreement, there is an increasing consensus that 'metabolomics' puts a greater focus on cellular or organ-level metabolic profiling and is particularly concerned with normal endogenous metabolism (Robertson, 2008).

Metabolic Footprinting

Metabolic footprinting or exometabolomics is the study of extracellular metabolites. It utilizes many methods from other metabolomics subfields, and has applications in the production of biofuels, bioprocessing, determining the mode of action of drugs, and studying intercellular relationships (Silva et al., 2015). While exometabolomics is concerned with the same analytical approaches used for profiling metabolites, such as liquid-chromatography mass spectrometry (LC-MS), nuclear magnetic resonance (NMR) and gas chromatography-mass spectrometry (GC-MS), exometabolite analysis presents specific challenges and is most frequently focused on investigating biological transformations of exogenous metabolite pools (Silva et al., 2015). Typically, these experiments are performed by comparing metabolites at two or more time points, for example, spent vs. uninoculated/control culture media; this approach can differentiate different

physiological states of wild-type yeast and between yeast mutants (Allen et al., 2003). Since, in many cases, the exometabolite (extracellular) pool is less dynamic than endometabolite (intracellular) pools (which are often perturbed during sample processing) and chemically defined media can be used, it reduces some of the experimental challenges of metabolomics (Čuperlović-Culf, 2014). Exometabolomics is also used to gain insight into the role of genes and pathways with genomic, transcriptomic (Rossouw et al., 2008) and proteomic data as a complementary tool. Additionally, exometabolomics can be used to quantify the polar molecules that an organism absorbs or releases and to measure the development of secondary metabolites (Chumnanpuen et al., 2014), (Kell et al., 2005). In contrast to authentic criteria, metabolites are defined rely on factual mass, retention time, and their MS/MS fragmentation patterns, as with traditional metabolomic measurements. Hydrophilic liquid chromatography for the evaluation of polar metabolites (McNamara et al., 2012) or reverse-phase (C18) chromatography for the measurement of non-polar substances, lipids and secondary metabolites (Gao and Xu, 2015) are usually used in chromatography. It is also possible to use gas chromatography-mass spectrometry to test sugars and other carbohydrates and to obtain full metabolic profiles (Sue et al., 2011). In functional genomics, exometabolomics play an important role in identifying annotations of unknown genes (Tambiev et al., 1989). In agricultural biotechnology, the study of PGPR (Plant Growth Promoting Rhizobacteria) was become much simpler to interpretate the research on plant root.

Metabolomics Workflow

Tissue, plasma, urine, saliva, cells, etc. are obtained from the first samples. Then, with the addition of internal criteria and derivatization, metabolites are also extracted. (Dettmer et al., 2006) Metabolites are quantified during sample analysis by liquid chromatography or gas chromatography coupled with MS and/or NMR spectroscopy. For metabolite function extraction, the raw output data may be used and further processed before statistical analysis such as PCA. To identify associations with disease states and outcomes, determine significant correlations, and characterize metabolic signatures with existing biological knowledge, many bioinformatic tools and software are available (Rasmiena et al., 2013).

Step 1: Method of Separation

Analytes in a metabolomic sample initially contain a highly complex blend. By separating certain analytes from others, this complicated mixture can be simplified prior to detection. Separation achieves different objectives: in this process, analytes that cannot be solved by the detector can be separated; ion suppression is decreased in MS analysis; the analyte's retention time serves as identity information. In NMR and "shotgun"-based approaches such as shotgun lipidomics, this separation step is not necessary and is often skipped. Gas chromatography (GC) is a widely used separation process for metabolomic analysis, especially when interfaced with mass spectrometry (GC-MS), (Ogbaga et al., 2016) GC offers high chromatographic resolution and can be used in combination with a flame ionization detector (GC/FID) or a mass spectrometer (GC-MS). The method is useful for identifying and quantifying small and volatile molecules (Gika et al., 2007) However, the necessity for chemical derivatization for many biomolecules is a practical limitation of GC, as only volatile chemicals can be analyzed without derivatization. Two-dimensional chromatography can be required in situations where greater resolving power is necessary.

Step 2: Method of Detection

Mass spectrometry (MS) is used after optional separation by GC, HPLC, or CE to classify and quantify metabolites. The first hyphenated technique to be developed was GC-MS. Identification leverages the separate patterns in which fragment analytes can be considered as a mass spectral fingerprint; libraries exist that allow a metabolite to be identified as per this pattern of fragmentation. MS is adaptive to both and it can be very precise. There are also a range of techniques that use MS as a stand-alone technology: the sample is infused with no prior separation directly into the mass spectrometer, and the MS provides both separate and metabolite detection with adequate selectivity. The analytes must be supplied with a charge and moved to the gas phase for analysis by mass spectrometry. The most popular ionization technique for GC separations is electron ionization

(EI), as it is susceptible to low pressures. EI also induces the analyte's fragmentation, all of which provide structural details while increasing the data's complexity and likely obscuring the molecular ion. Chemical ionization of atmospheric pressure (APCI) is an atmospheric pressure method that can be extended to all the separation techniques above. APCI is a slightly more aggressive ionization form of gas phase ionization than ESI, which is ideal for less polar compounds. With new MS techniques focusing on rising sensitivity, minimizing context, and reducing sample preparation, surface-based mass analysis has seen a revival in the past decade. Current MS technology continues to question the capacity to evaluate metabolites directly from biofluids and tissues, primarily because of the limitations imposed by the complexity of these samples, which contain thousands of metabolites. Nanostructure-Initiator MS (NIMS) (Northen et al., 2007), (Woo et al., 2008) is a desorption/ionization approach among the technologies being developed to address this problem, that does not require the application of the matrix and thus facilitates the detection of small molecules (i.e., metabolites). However, the need for a MALDI matrix may also add substantial history to <1000 Da, which complicates the study of the low-mass range (i.e., metabolites). The size of the resulting matrix crystals also limits the spatial resolution that can be achieved in the imaging of tissues. Several other matrix-free desorption/ionization methods (MALDI) have been extended to the study of biofluids and tissues because of all these constraints.

Applications of Metabolomics

In Plant Biotechnology

In many resistance and stress responses, plant metabolites are involved and also contribute to the color, taste, aroma, and fragrance of fruits and flowers (Bino et al., 2004). As we described earlier, an organism's biochemical phenotype is the ultimate outcome of genotype-environmental stimulus interactions, but it is also modulated by intracellular physiological variations which are characteristic of homeostasis (Weckwerth et al., 2003). It is therefore important to recognize and quantify metabolites simultaneously in order to understand the dynamics of the metabolome, to analyze fluxes in metabolic pathways and to decipher the position of each metabolite following different stimuli in plants (Fiehn et al., 2003). Biotechnological techniques are often used to modify metabolism for the optimal development of plant metabolites that directly benefit human health and plant growth. For example, golden rice which is a transgenic line of Oryza sativa that was genetically engineered in the edible parts of rice to biosynthesize β-carotene, a pro-vitamin A. (Ye et al. 2000; Yonekura-Sakakibara and Saito 2009). The introduction of snapdragon transcription factors into tomatoes increased the yield of anthocyanins with health-protective properties (Butelli et al. 2008). However, many similar methods do not lead directly to the expected results, for example, overexpression in transgenic petunia of foreign S-linalool synthase won't lead to the expected free linalool accretion, but led to the accretion of S-linalyl-β-d-glucoside (Lucker et al. 2001). These unusual findings indicate that plant metabolism is regulated by highly complex regulatory systems and also indicate the need for further accurate plant metabolism information. In this sense, metabolomics plays an important role in the field of molecular biotechnology, where the expression of engineered genes modifies plant cells. Metabolomic analysis provides us with in-depth cellular metabolism information through a metabolome snapshot, often combined with other 'omics' data (Oksman-Caldentey and Saito 2005; Saito and Matsuda 2010). Metabolomics is among the methods of omics which can be used to obtain detailed metabolite details. It seeks to understand in measured samples the global state of metabolism. Genomics was the first to arise from the omics experiments used in plant sciences and revealed genome sequences of many species, including Arabidopsis (Arabidopsis Genome Initiative 2000) and rice (Goff et al. 2002; Sasaki et al. 2002; Yu et al. 2002; International Rice Genome Sequencing Project 2005). Metabolomics is among the methods of omics which can be used to obtain detailed metabolite details. It seeks to understand in measured samples the global state of metabolism. Although, Genomics was the first to arise from the omics experiments used in plant sciences and revealed genome sequences of many species, including Arabidopsis (Arabidopsis Genome Initiative 2000) and rice (Goff et al. 2002; Sasaki et al. 2002; Yu et al. 2002; International Rice Genome Sequencing Project 2005).

In Oncology

Oncology is one of the most relevant uses of metabolomics in the study of human diseases. Because tumor cells are highly proliferative and have high transcription and translation speeds, as well as higher energy demand, cells compared to normal, they have unique metabolic requirements, often losing many regulatory functions (Hanahan et al., 2000). Thus, the use of metabolomics in predicting the presence of tumor cells is one of the greatest challenges in medicine. Initially, preclinical analyses have identified potential metabolic biomarkers for the identification and/or evaluation of the efficacy of anticancer drugs in cancer, accompanied by confirmation of these biomarkers in biofluids like blood, urine, prostatic and secretions, (Serkova et al., 2009). In certain cases, however, it is extremely useful to integrate metabolomics with other genomic and/or proteomic techniques for both cancer detection and cure. The global quantitative evaluation of endogenous metabolites inside a biological system is Metabolomics, an omic science in systems biology. Identification of metabolites is performed in cells, tissues, or biofluids by either nuclear magnetic resonance spectroscopy or mass spectrometry, either individually or grouped as a metabolomic profile.

There is potential for the metabolome to have a wide variety of uses in oncology, along with the early detection and diagnosis of cancer and as both a predictive and pharmacodynamic marker of drug impact. Despite this, there is a lack of information about metabolomics and misunderstanding about its methodological methods, technological problems, and therapeutic research in the oncology community. Biomarkers are commonly used in medical research for diagnostic or forecasting purposes. Using animal and human cell cultures, quantitative metabolomic biomarkers for cancer diagnosis and/or treatment efficacy evaluation are typically investigated preclinically, accompanied by validation in biofluid or tumor tissue. Biomarkers are increasingly used to define, verify and optimize drug strategies and agents in the early clinical development of those agents; to evaluate and confirm the process of drug action as a pharmacodynamic end point; and to predict or control responsiveness to medication, toxicity and tolerance (Perk et al., 2004). Nevertheless, the omics sciences are compatible as "upstream" changes in genes and proteins are evaluated "downstream" as cell metabolism changes (Griffin et al., 2004), (Boros et al., 2005). However, the reverse is that metabolomics is also a terminal view of the biological system, not allowing genes and proteins that are increased or decreased to be portrayed. In the scope of the immediate surroundings, metabolomics enables a global evaluation of the cellular state, taking into consideration genetic regulation, altered enzyme kinetic activity and changes in metabolic reactions (Griffin et al., 2004), (Mendes et al., 1996) and (Mendes et al., 1992).

Cancer is an infection that adjusts the metabolism of a cell and metabolomics approaches are being utilized to all the more likely comprehend these adjustments in cancer metabolism (Beger et al., 2013). Both open and centered metabolomics of host, approaches alongside imaging strategies can be utilized to screen metabolism in cancer for both symptomatic and predictive biomarkers (Vander et al., 2011). Metabolomics has shown a great deal of promise for personalized medicine and cancer diagnostics; be that as it may, introductory outcomes are as yet test and it needs to beat numerous difficulties to be completely executed and arrive at its maximum capacity (Fiehn et al., 2001).

The difficulties incorporate universally acknowledged quality control guidelines, identification of obscure pinnacles, approval considers, the capacity to separate between radiation harm and adverse effects of drug cases, the expansion of clinical metadata to metabolomics, sharing of clinical metabolomics information in the facility with regulatory agencies, procuring and deciphering the clinical metabolomics information, and executing NMR spectrometers and MS in the clinical conditions (Chen et al., 2019). The modified metabolism in tumors is prompting the improvement of numerous cancer drug treatments that focus on the changed metabolic pathways, enzymes, or carriers engaged with cancer. Hence, metabolomics examinations of biofluids isolated from cancer patients and medical involvements to cancer will keep on being valuable in giving a superior understanding of the perplexing idea of cancer and for giving data to the clinician about the patient's reaction to medical interventions to cancer. In recent advances, emerging metabolomics applications for in vivo isotope tracking and metabolite imaging, both of which seek to improve

our knowledge about the role of cancer metabolic reprogramming (Kaushik et al., 2018).

Result and Discussion

In order to produce energy and biosynthetic precursors for development, metabolism promotes various biological aspects of cell, including the breakdown of complex sugar sources such as carbohydrates, lipid sources like fats, and amino acids. In cancer cells, these essential characteristics of cellular metabolism are reconfigured to endorse their dysfunctional rate of inflation and propagation. In several fields, such as biochemistry, genetics, physiology and bioinformatics metabolomic studies can be applied. Metabolomics has the ability to have a significant effect on numerous biological fields, including human health, plant biotechnology, toxicology, and pharmacology. The interpretation and understanding of the data collected includes the use of bioinformatics, as well as the incorporation of genomic and proteomic analysis data. Metabolomics has the potential to help us better understand the molecular mechanisms of disease with the advancement of more responsive technologies and also analytical methods for statistical analysis and data interpretation. Metabolomics has the potential to help us better understand the molecular mechanisms of disease with the advancement of more responsive technologies and also analytical methods for statistical analysis and data interpretation. Furthermore, the detection and analysis of new biomarkers identified in oncology would allow several diseases to be identified and prevented, as well as new drugs to be discovered. In oncology, however, it is also important to assess other biomarkers, such as protein markers, as well as to determine the physiological condition for management and therapy.

CONCLUSION

Metabolomics has gained significance in biological science in human disease assessment, anti-viral therapy, transgenic plant research, food quality, disease resistance enhancement, and herbicide or salinity tolerance and PGPR studies. In addition, the combination of the three omics and biology of systems is an excellent technique for the enzymes involved in the exploration of unknown metabolic pathways. Furthermore, in the efforts made to enhance human health, metabolomics applied to the study of plants is extremely significant. The alteration of plant metabolic pathways could contribute to the development of new drugs that can be used for the treatment of various diseases, as there are many cases where the modulation of various metabolic pathways has resulted in an increase in the production of a particular metabolite. In the other aspect of oncology, Understanding the fundamental metabolic structure of cancer can possibly give the establishment to the improvement of novel methodologies focusing on tumor metabolism. In cancer diagnosis and treatment with the help of precision medicine, metabolic markers can play a significant t role in understanding the alteration occurring in various pathways, thus making metabolomic study in oncology one of the dynamic features so to be applied in personalized and precision medicine.

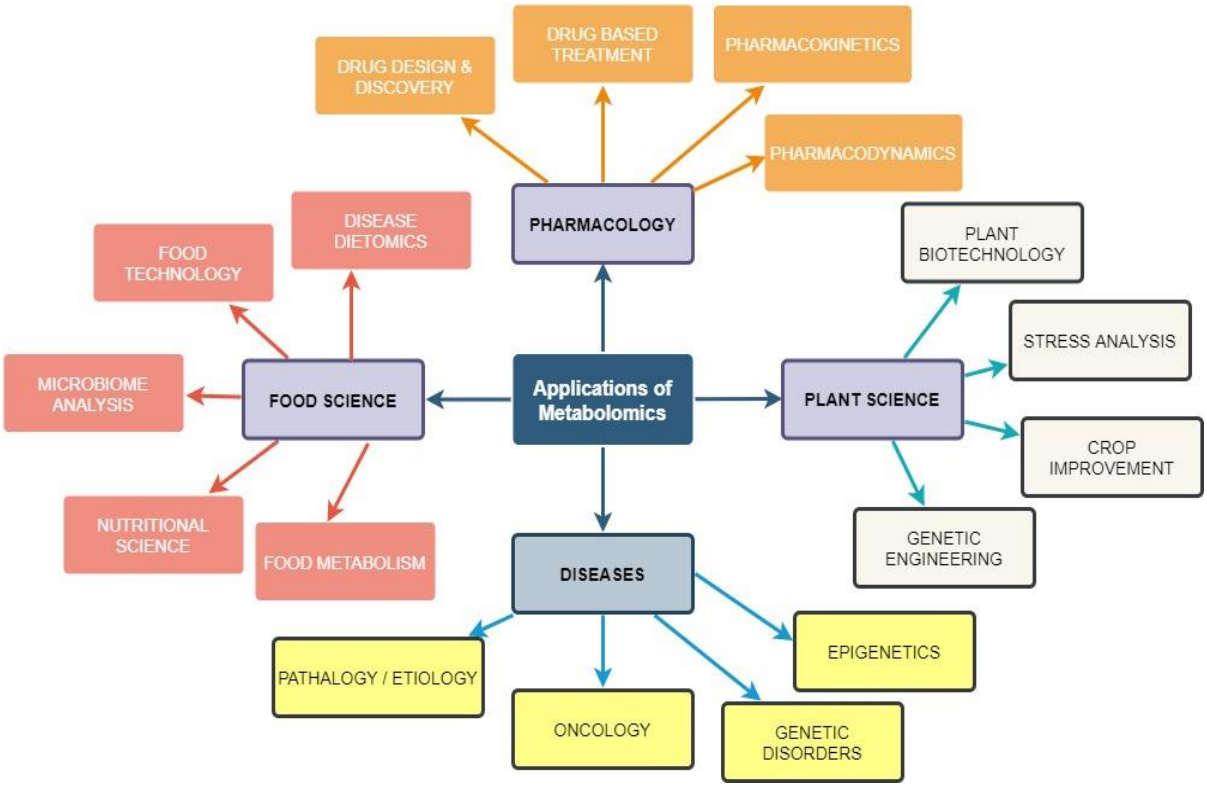

FIG. 1. REPRESENTATION OF VARIOUS APPLICATIONS OF METABOLOMICS INCLUDING PHARMACOLOGY, PLANT SCIENCE, FOOD SCIENCE AND DISEASES.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

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