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REVIEWS: CURRENT TOPICS

Analytical metabolomics: nutritional opportunities for personalized health☆,☆☆

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Abstract

Nutrition is the cornerstone of health; survival depends on acquiring essential nutrients, and dietary components can both prevent and promote disease. Metabolomics, the study of all small molecule metabolic products in a system, has been shown to provide a detailed snapshot of the body's processes at any particular point in time, opening up the possibility of monitoring health and disease, prevention and treatment. Metabolomics has the potential to fundamentally change clinical chemistry and, by extension, the fields of nutrition, toxicology and medicine. Technological advances, combined with new knowledge of the human genome and gut microbiome, have made and will continue to make possible earlier, more accurate, less invasive diagnoses, all while enhancing our understanding of the root causes of disease and leading to a generation of dietary recommendations that enable optimal health. This article reviews the recent contributions of metabolomics to the fields of nutrition, toxicology and medicine. It is expected that these fields will eventually blend together through development of new technologies in metabolomics and genomics into a new area of clinical chemistry: personalized medicine.

Keywords: Metabolomics; Clinical chemistry; Nutrition; Toxicology; Personalized medicine

1. Introduction

It is well known that nutrition is the cornerstone to health. Observational and anecdotal data have clearly documented that a poor diet, however crudely defined, promotes obesity, diabetes, atherosclerosis, hypertension, malignancy, osteoporosis, inflammatory disease, infectious disease, etc. All of these conditions are related to metabolic imbalances [1] that are not clearly understood. Indeed, within seemingly similar environments, some individuals suffer catastrophic failures in health, while others achieve unprecedented health and longevity. The strength of the epidemiologic association between diet and health has highlighted science's inability to understand how nutrients affect individual metabolic regulation, as well as the reason for the variation of these diseases within the apparently normal population. Investigating this individual variation in order to provide a more personal set of measures and solutions, such as an individualized system for metabolomic assessment, would establish a new framework to enhance human health through increasing the efficacy and safety of diets. Such a framework would enable dietetics professionals to quickly and accurately assess the nutritional status of an individual, plan an appropriate intervention and then monitor compliance, progress and side effects. All this could be done within the context of an individual's environment, lifestyle, development, gut microbiome, and nutrition and health status [2] (Fig. 1).

Current methods of measuring nutrition and health are rooted in clinical chemistry, a branch of pathology that involves evaluating body fluids in the context of human health and disease. Its origins date to ancient times where, for example, qualitative assessments of urine based on color, odor and taste were used to diagnose conditions such as diabetes. The growth and development of clinical chemistry as a full-fledged science and companion industry occurred in the 19th and 20th centuries when the combination of analytical tools to measure small molecules, hormones, fatty acids and other substances, together with an understanding of conditions that underlie variations in those substances in urine and blood, was brought to the routine practice of aiding physicians in diagnosing disease. This has led to gold standard tests for many diseases. However, the limited number of substances that are easily measured, the fact that changes in only one or two variables may indicate a variety of conditions and the inability to discover and relate subtle changes in some metabolite concentrations to specific disorders have meant that clinical chemistry has been, to some extent, lacking in its specificity. Thus, for centuries, diagnostics has been somewhat of an art, and, in the context of disease, a patient's fate may be predicated on a physician's mastery of that art.

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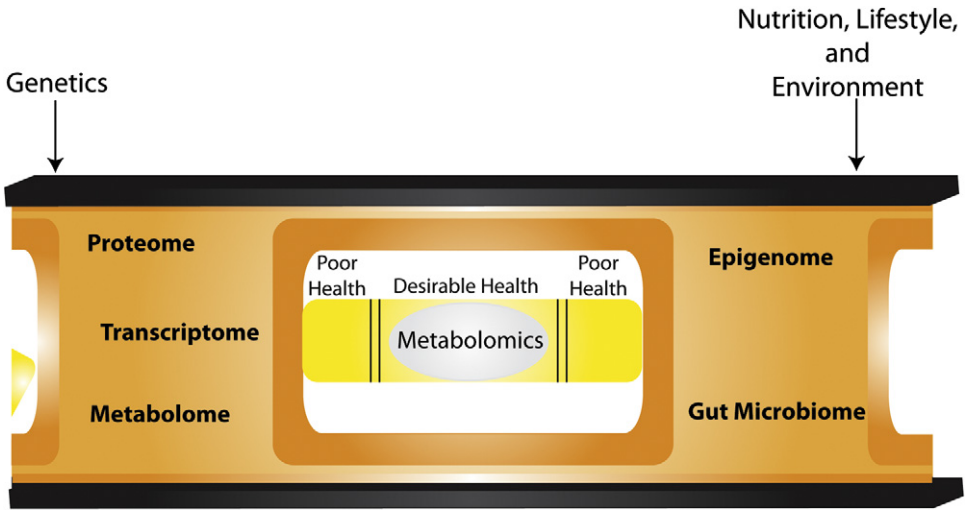

Fig. 1. The level of health. Overall health is heavily influenced by genetics. However, diet, lifestyle and environment can change the epigenome, gut microbiome and, by association, the transcriptome, proteome and, ultimately, the metabolome. When the combination of genetics and nutrition/lifestyle/environment is not properly balanced, poor health is a result. Analytical metabolomics is becoming a major tool for detecting small changes in the gut microbiome, epigenome, transcriptome, proteome and metabolome, which may ultimately help guide nutritionists to develop personalized nutritional strategies, helping people achieve desired health outcomes within their genetic framework.

The metabolome refers to the complete metabolite composition of a system such as a cell or organism. Metabolomics is essentially the fusion of the measured metabolome with chemometrics to identify chemical changes that may indicate a disease state or a response to external stimuli. The ability to quickly measure scores of metabolites from a single sample is largely due to technological advances particularly in the past decade in analytical techniques such as nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS). (For in-depth reviews of these technologies, see Refs. [3,4]) Rather than measure just one or two metabolites at a time, tens to hundreds to thousands of metabolites, through global or targeted means, can be measured simultaneously in a single sample, and those metabolites that change concentration with a specific condition or perturbation can then be statistically identified. Through multivariate statistical analysis, key, and potentially subtle, changes in chemical composition of biofluids or tissues can provide detailed information of exactly what is happening in the system — a powerful tool in the future of medicine, given that most diagnostic clinical assays look for small molecules and that many identified genetic disorders involve diseases of small molecule metabolism.

Further advances in metabolomics technologies, including advances in instrumentation and software, and their application to a wide range of health fields, including nutrition, toxicology and medicine, may soon help us realize the ultimate goal of personalized health care.

2. Metabolomics in nutrition and toxicology

It has long been known that nutrition can both prevent and promote disease. But we still do not understand many of the links between an individual's diet and specific health outcomes — why one person develops type 2 diabetes and another, with the same diet, does not, or why one person needs more of a particular micronutrient than another to avoid deficiency. Metabolomics can help track the interaction between nutrients (and toxins) and human metabolism, as well as the involvement of the genome and the gut microbiome, in overall human health.

Standard nutritional studies can benefit from the tools of metabolomic analysis. Already, it has been shown that metabolomic tracking can reveal specific components of an individual's reported dietary intake: general meat intake is associated with increased levels of anserine and 1-methylhistidine [5], red meat with *O*-acetylcarnitine and vegetables with phenylacetylglutamine [6]. Additionally, in a recent study of adult men, reported intake of polyunsaturated fatty acids was inversely associated with serum concentration of saturated fatty acid chains of glycero-phosphatidylcholines [7]. On a population level, metabolomics may be used to evaluate food frequency questionnaires and thus improve epidemiological studies [5]. Metabolomics could also help detect and prevent nutrient deficiencies. A depletion–repletion study of choline showed that a person's metabolomic profile at baseline could predict whether or not he or she would develop liver dysfunction as a result of inadequate choline intake [8].

As metabolic sciences have examined diet in both greater detail and diversity, some astonishing discoveries have begun to link food with a range of health outcomes. For instance, omega-3 fatty acids from fish oil have been shown to enhance a variety of protective processes [9], all of which are linked to protection from deleterious health outcomes such as cellular damage, tissue destruction, inflammation and pain. The number of calories consumed has also been shown to have significant impact on health. Too many can lead to obesity, whereas a sharp restriction (still with enough nutrients to satisfy basic nutritional needs) can increase life span and greatly reduce the incidence of disease [10] (for review, see Refs. [9,11]). Mechanistic studies over the past decade have identified the underlying cellular targets and biological processes that result from caloric restriction. Specific food components have now been found that can act on those same targets and replicate an identical outcome — longer life span [12]! Current research in plant metabolomics can help breed better varieties and develop better processing strategies, so that our food source has increased abundance and bioavailability of beneficial compounds [13].

Several studies of obesity have revealed substantial metabolomic differences between obese and lean subjects. In one study, it was observed that the strongest difference in metabolite concentration between the obese and lean human subjects involved a combination of the branched-chain amino acids, methionine, glutamate/glutamine, phenylalanine, tyrosine as well as the acylcarnitines [14]. Kim et al. concluded that the metabolomic difference observed between lean and overweight/obese subjects resulted from abnormal metabolism of specific branched-chain amino acids, aromatic amino acids and fatty acids [15]. Using an obese rodent model, it was suggested

that a conditional host genetic involvement in selection of the microbial species could be responsible for the lean and obese animal metabolic phenotypes that could be ultimately linked to their individual microbiomes [16]. And, in a study of adolescent Scandinavians [17], it was shown that gender and the plasma triglyceride content are major factors causing variation in the plasma metabolome, with no effect of weight, height or body mass index.

An individual's metabolome changes by the minute, reflecting shifts from anabolism to catabolism or reactions to particular stimuli, and it can change more gradually, reflecting the onset of disease. In addition, elements of the profile remain constant over the course of weeks and even years [18,19]. This is due, in part, to the constancy of an individual's genetic makeup and lifestyle/environment. Holmes et al. suggest that common diets, gut microbes, medicinal practices, genetics and other lifestyle and environmental factors give rise to regional metabolomic phenotypes. A study of people living in Japan, northern China, southern China and the West (US and UK) reported significant differences between the urinary metabolic profiles based on geography [20].

Normal growth and development influence metabolomic patterns. Specific profile elements can even be seen before birth and have been shown to indicate the reproductive potential of embryos, significant developmental changes or normal versus abnormal fetal development [21–23]. The metabolomics of amniotic fluid and placental tissue may be able to better predict conditions such as preeclampsia [24] and preterm labor and delivery [25]. Metabolomes after birth are telling as well: children, adolescents, young adults and older adults have all been shown to have specific metabolomic differences [26,27]. Gender and physical fitness appear to play a role in the metabolome, as blood metabolomes differ not only between professional athletes and control subjects, but also among athletes of different exercise seniority and training stages [28]. Understanding these differences is important, not only to define health or lack thereof, because they have the potential to be confounding factors in clinical studies.

The variable metabolome seems distant from the genome, which remains fixed throughout an entire life. Yet changes in gene expression are discernible in the metabolome. The field of nutrigenomics has emerged in this context to understand how gene expression relates to metabolism: both how particular genotypes cause particular phenotypes and how changes in the diet cause changes in gene expression. While there are numerous studies that have identified genetic polymorphisms that convey risks for developing certain diseases, genetic measures alone have not yet yielded definitive information on the processes that result in disease. However, combining genetic information with molecular details of individual phenotypes is beginning to provide insights into underlying mechanisms.

The goal of nutritional metabolomics is to understand what happens to entire metabolomes with changes in diet and ultimately to map metabolic regulation problems with diet as the key input variable to metabolism itself. Many studies are beginning to promote this goal and show a clear link between specific dietary elements and changes in the metabolome. For instance, green tea consumption was shown to cause an immediate change in the concentrations of metabolites involved in glucose metabolism, the tricarboxylic acid (TCA) cycle and amino acid metabolism in humans [29]. Another recent study provided proof that variations in genes coding for certain enzymes cause specific changes in the concentrations of a comprehensive set of naturally occurring blood serum metabolites in humans and that these changes match the biochemical pathways in which the enzymes are active [30]. Understanding the specific metabolomic changes associated with these diets may help elucidate the underlying mechanisms.

Metabolomic studies can also indicate the role of gut microflora in health. Indeed, evidence already exists for the role of microflora in general metabolism. For example, in a study by Martin et al., it was shown that feeding pro-, pre- or synbiotics could induce microbial changes in mice and that microbial activity directly correlated with dietary calorie recovery, fat absorption and lipid metabolism [31]. In healthy human subjects, moderate dark chocolate consumption was shown to modify the host and gut microbial metabolism, reduce the urinary excretion of catecholamines and the stress hormone cortisol, and partially normalize stress-related differences in energy metabolism and gut microbial activities [32]. Microbe effects can also be linked specifically to cardiovascular disease (CVD). For instance, arginine supplementation was shown to result in decreased fat deposition and increased protein accretion in growing pigs — an outcome that may proceed from changes in the intestinal bacterial metabolites formate, ethanol, methylamine, dimethylamine (DMA), acetate and propionate, as well as the pig's serum concentrations of glycerophosphocholine and *myo*-inositol [33]. A study of the human intestinal metabolome, before and after the microbiome was disrupted by antibiotics, showed changes in levels of over 87% of the metabolites detected and indicated significant changes in host metabolic processes, such as bile acid and steroid hormone synthesis. A better understanding of these interactions could speed the discovery of appropriate therapeutics [34].

Oncology, and specifically dietary means of cancer prevention, is another area in which metabolomics studies are important. Indeed, epidemiologic studies comparing dietary patterns between countries of low and high incidence for particular cancers have shown that dietary modifications and interventions have the potential to significantly lower cancer risk and its associated complications [35]. Combined with metabolomics, an understanding of the link between dietary practices and cancer may be elucidated. Both *in vitro* and *in vivo* studies have suggested that a high consumption of antioxidant-rich fruits and vegetables can reduce the risk of cancer without adverse effects. The natural antioxidant vitamins, flavonoids, tocopherols, polyunsaturated fatty acids, phenolic phytochemicals and others from food components are being extensively studied as they are generally perceived as safe, “natural” (versus medicinal) chemopreventive agents based on their long history of use in the diet and/or as traditional medicines. Understanding how these bioactive compounds work will be important as we develop better supplements and/or diets.

Metabolomics is also important in toxicology for understanding how exposure to chemicals and the environment affects gene and protein expression as well as cellular and system-wide functioning. Indeed, a certain amount of overlap between the two fields surfaces when we consider the use of diet-derived compounds at pharmacological concentrations. Returning to the example of cancer-fighting compounds, it is becoming increasingly apparent that their isolation and use could have deleterious effects at pharmacological concentrations. There have been a number of case reports of hepatotoxicity related to the consumption of high doses of tea-based dietary supplements [36], and in a study by Walsh et al., acute changes in human urinary metabolomic profiles were observed after the consumption of dietary phytochemicals [37]. Even essential nutrients, while necessary at certain levels, can become damaging at excessive levels. For instance, several supplementation studies with vitamins and some phenolics have revealed no evidence of benefits and in some cases have caused DNA damage [38]. Still, approximately 38%–51% of American men and women 40 years or older use dietary and nutritional supplements on a regular basis [39]. Metabolomics can also help illuminate the mechanisms by which these compounds function and thereby assist researchers in making nutritional recommendations for their intake at dietary and pharmaceutical levels [40]. Much work has been done using metabolomics to better understand various aspects of traditional Chinese medicine, including herbal and mineral medicines as well as acupuncture [41].

Pharmaceuticals can have effects ranging from purely beneficial to mild oxidative stress to critical organ damage, all due to broad metabolic perturbations. Substantial evidence exists from studies done in rats. For instance, preliminary metabolomic analysis of rats has shown that ibuprofen and other nonsteroidal anti-inflammatory drugs cause gastrointestinal damage [42], that melamine causes perturbations in the urinary metabolome [43], and that cinnabar (a traditional Chinese mineral medicine) causes disturbances in energy and amino acid metabolism, changes in the gut microflora environment, and liver and kidney injury [44]. Acute and chronic doses of acetaminophen were seen to result in increased oxidative stress in rats, as evidenced by a decrease in antioxidants and energy-related metabolites [45]. Early detection of such alterations by metabolomic analysis suggests that physiological damage could be screened for and possibly prevented.

An important focus of the toxicological effects of dietary supplements and pharmaceuticals should therefore be on the early detection of kidney and liver damage. It has been shown that under nephrotoxic conditions, amino acid excretion increases (aminoaciduria) due to impaired reabsorption by the renal tubules, increased cellular turnover or increased permeability of the glomerular membranes. It should be noted that hyperaminoaciduria is a somewhat nonspecific symptom; it can also signal conditions such as chronic liver disease and can be induced during critical illness. Nevertheless, rats treated with a nephrotoxin developed aminoaciduria, which could be clearly observed through urinary metabolome analysis [46]. Importantly, the metabolomic variance could be observed prior to any histopathological kidney damage in rats, making this type of study particularly important for the pharmaceutical industry. It has been shown that metabolomics can detect problems earlier than classical methods such as histopathology, clinical chemistry, hematology and urinalysis [47], so metabolomic analysis could make drug testing safer and more efficient and could help avoid late-stage attrition during pharmaceutical drug development. For a review of metabolomic detection of drug-induced kidney injury, see Ref. [48].

Metabolomics also has implications for noningested toxins. Specific changes in urinary profiles after exposure of mice to sublethal doses of ionizing radiation resulted in the observation of deaminated purines and pyrimidines at the expense of aminopurines and aminopyrimidines in the first 24 h after exposure [49]. Another study showed changes in specific lipids in the plasma of rats after exposure to ionizing radiation [50]. A recent study by Sumner et al. demonstrated that urinary metabolic profiles could differentiate not only between pregnant rats that received a vehicle or a low or a high dose of the chemical butyl benzyl phthalate 3 weeks after gestational exposure but also between pups born to dams in each group, suggesting that a mechanistic link could be made between low levels of environmental exposure and disease/dysfunction [51].

The gut microbiome plays an important role in modulating the effects of toxins, as illustrated in a study on the influence of gut microbiota on the toxicity and metabolism of hydrazine. Using conventional and germ-free mice, it was shown that both groups excreted identical toxin metabolites. However, toxicity was more severe in the germ-free cohort, indicating that the presence of bacteria in the gut altered the nature and extent of response to hydrazine [52]. Several studies that are now under way are attempting to understand the long-range effects of gut microbiota modulation in various diseases and to assess the depth of symbiotic control in complex organisms. A comparison of urinary profiles of twin sisters indicates that they are very similar, but not identical, suggesting that although genotype plays a role in defining an individual metabolic phenotype, the latter is modulated by both gut microflora and response to external stimuli. It is now being postulated that an individual metabolic phenotype be considered a metagenomic entity linking the gut microbiome and host genome [19].

Given the extensive interplay between nutrients, toxins, genes and gut microbes, the fields of nutrition and toxicology will greatly benefit from a tool that allows more accurate measurement of the genotype–metabotype relationship and a more complete understanding of the role that diet plays in health status.

3. Metabolomics in medicine

Traditionally, health has been defined by the lack of observable disease, and disease has been characterized as having a single cause yielding a single diagnostic target; this view has informed both diagnostics and therapeutic solutions. Individuals are generally diagnosed for various diseases using a large battery of tests, each for a particular biomarker whose presence reflects the explicit presence or consequence of pathogens, toxins, dysregulated cells or nutrient deficiencies. Many of these tests are neither sensitive nor specific enough to unequivocally provide an accurate diagnosis. Now, considerable research has linked metabolic imbalances to human disease and has highlighted the fact that dysregulation of metabolism subtly alters entire pathways, not a single target. It has been shown that analytical measurement of a large number of metabolites in biofluids such as urine and serum can provide more clues to a health or disease state than traditional clinical laboratory tests, which rely on the measurement of only a small number of molecules. Thus, metabolomics, by simultaneously measuring a large number of metabolites, may provide an early indication of a particular condition and potentially prevent irreversible deleterious consequences. Studies at the level of pathways (systems biology) can help clarify exactly what changes to the metabolome are associated with disease.

Cardiovascular disease presents a particularly rich area of study, as many of the disease mechanisms are poorly understood. It is known that specific dietary components can result in or protect against CVD. For instance, the amount of milk fat in the diet was shown to correlate positively with the degree of atherogenicity in hyperlipidemic hamsters [53], while plant sterol esters enriched with stearate appeared to lower low-density lipoprotein cholesterol in humans [54]. Consumption of whole-grain rye versus non-whole-grain wheat diets was shown to result in major differences in the plasma metabolome of hypercholesteremic pigs, specifically in betaine levels [55]. There is much interest in how diet impacts cardiovascular health; by providing a more fine-grained picture of disease development, metabolomics could provide clues about long-term outcomes much sooner.

Metabolomics is also enhancing our understanding of CVD progression. For instance, it has been used to uncover novel biomarkers for acute myocardial ischemia in humans [56], and patients with acute coronary syndrome showed specific differences in plasma metabolites as compared to healthy subjects and patients with stable atherosclerosis [57]. A comparison of hypertensive and control rats has shown significantly different levels of several plasma organic, amino and fatty acids [58]. In animal models of atherosclerosis, changes in certain plasma and urine metabolites were shown to be altered upon development of the disease [59], and a time-dependent progression from normal to hypercholesterolemia and early atherosclerosis could be monitored over time [60]. Treatment can also be tracked and better understood: a rabbit model of hypercholesterolemia has been used to assess the pleiotropic effects of simvastatin (such as its antioxidant effects) in addition to its main action as an inhibitor of cholesterol synthesis [61].

Metabolomics is providing insights into diabetes, a pressing public health concern. Oresic et al. studied children from birth to onset of type 1 diabetes. They determined that individuals who developed diabetes had a number of metabolic signals at birth (reduced serum

levels of succinate and phosphocholine), throughout follow-up (reduced levels of triglycerides and antioxidant ether phospholipids) and just before what is traditionally thought of as onset of disease (increased levels of proinflammatory lysoPCs several months before seroconversion to autoantibody positivity). These distinct metabolomic profiles may be early signals of diabetes and suggest that autoimmunity is a relatively late response to the early metabolic disturbances [62]. Early metabolomic measurement could have profound impacts on the way that we approach treatment of diseases, and potentially allow for prevention or reversal.

Type 2 diabetes has been studied as well. It was shown that a high-fat diet designed to induce insulin resistance produces specific plasma metabolic differences in mice [63] and increased β-oxidation and decreased TCA cycle intermediates in skeletal muscle in rats [64]. Furthermore, skeletal muscle insulin resistance in mice was linked to lipid-induced mitochondrial stress [64]. It was also shown through metabolomic analysis of human serum samples that different treatments can result in different effects on physiology, yielding a novel, non-glucose-based evaluation strategy for the systemic treatment effect in type 2 diabetes mellitus patients [65].

Chronic stress may also modulate metabolomic profiles. In a human study by Rezzi et al., the metabolic events associated with background stress were shown to influence the response to novel incoming stress stimulus (a cold pain test) in healthy subjects [66]. The novel stress caused differences in energy and lipid homeostasis, observable in urine and plasma metabolite levels. Cold pain appeared to increase gut permeability as determined by mannitol and xylose levels, with the rate of plasma clearance dependent on the background stress level and gender. In addition, cold pain modulated the levels of circulating ketone bodies, TCA cycle intermediates, glucose, and glucogenic alanine and lactate [66]. Furthermore, results from rats suggested that the stress-induced metabolic perturbations were reversible and nonspecific [67]. In another rat study, specific biomarkers of chronic mild stress were found and may be associated with altered amino acid metabolism, energy metabolism and glycometabolism. The metabolomics of stress may even lead to a deeper understanding of the biochemistry behind psychological conditions such as depression and provide both earlier diagnosis and preventive care [68].

Celiac disease (CD), a multifactorial disorder with genetic and environmental components, illustrates the complex interplay between chronic disease and gut microflora. Celiac disease is an immune-mediated enteropathy triggered by the ingestion of wheat gluten or related rye and barley proteins in genetically susceptible individuals. The metabolome for CD has three components: one directly related to malabsorption, one related to energy metabolism and the third related to alterations of gut microflora and/or intestinal permeability [69]. In a human study by Jansson et al., it was determined that those metabolites that distinguished celiacs from normal subjects came from pathways involved in the metabolism and/or synthesis of amino acids, fatty acids, bile acids and arachidonic acid. Several metabolites were positively or negatively correlated to the disease phenotype and to specific microbes previously characterized in the same samples. Previous studies from the same group showed that levels of several gut microbial communities differed significantly between individuals with CD in the ileum (ICD) versus colon (CCD) and versus healthy individuals; in particular, ICD individuals had lower levels of *Faecalibacterium prausnitzii* and *Escherichia coli* relative to the other two groups. However, there was no clear distinction between the microbial community profiles in healthy individuals and those with CCD [70].

Other intestinal disorders have also been studied. For example, increases in urinary xanthurenic acid and α-carboxyethyl-hydroxychroman (α-CEHC) glucuronide were associated with increased colon inflammation in mice, making them potentially useful as biomarkers [71]. In a mouse model of colitis, metabolomic analysis was able to reveal the presence as well as the degree of the disease. Additionally, it suggested that glutamine supplementation might be used to treat the condition. Indeed, this therapy reduced colonic inflammation, and the progress could be tracked through metabolomics [72]. Further insights like these could lead to novel dietary or probiotic treatments for a range of intestinal disorders.

Cancer cells produce conspicuous metabolomic profiles, as they have evolved high glucose consumption and amino acid accumulation, while retaining tissue-specific dependency on aerobic respiration represented by TCA intermediate and nucleotide levels [73]. This results in many interesting differences between cancerous and noncancerous tissues. For example, colon tumor tissue has significantly lower glucose concentration, and colon and stomach tumor tissues have high lactate and glycolytic intermediate concentrations, as compared to healthy tissues [73]. Additionally, the intermediates of the TCA cycle and lipids were found to be down-regulated in colon cancer tissue, whereas urea cycle metabolites, purines, pyrimidines and amino acids were found at higher levels compared to normal colon mucosa [74]. Interestingly, no organ-specific differences were found in the levels of TCA cycle intermediates upon comparison of colon and stomach cancer tissues [73]. Comparing profiles of fecal water extracts revealed a low concentration of short-chain fatty acids (acetate and butyrate) in the colorectal cancer patients as compared to healthy individuals, whereas concentrations of proline and cysteine were higher in samples from colorectal cancer [75].

Other types of cancer tissue samples can be distinguished from controls, such as lung [76] and esophageal [77]. In some cases, the sample can be positively identified, as has been shown with breast, ovarian and cervical cancers [78] and with oral squamous cell carcinoma, oral lichen planus and oral leukoplakia in saliva samples [79]. Metabolomics could be especially powerful in providing earlier diagnosis of cancer [80] and in distinguishing between metastatic and nonmetastatic cancers; early results have been shown in pancreatic [81] and gastric cancer [82].

Detection and diagnosis of infectious disease are particularly hot areas of discovery. In two recent publications by the same group, it was determined that the specific microbe causing an illness, in this case pneumonia, could be distinguished from other microbes with a sensitivity of 86% and a specificity of 94% [83,84]. It was also shown that lymphocytic choriomeningitis virus infection could be monitored in mice by metabolomics on blood [85].

Disease, whether chronic or acute, bacterial, viral, cancerous or autoimmune, produces unique fingerprints. Compared with traditional clinical chemistry, the results from metabolomics studies have the power to revolutionize medicine by providing more information to physicians than ever before.

4. Future directions

Two pediatric cases illustrate the potential of personal metabolomics: an 8-year-old with epilepsy and an 11-year-old with malignant lymphoma. Both were being treated with methotrexate, and their observed metabolic profiles were identical to those of phenylketonuria patients, who lack a hepatic enzyme responsible for metabolizing phenylalanine. Interestingly, the metabolic profiles returned to normal when the patients were not receiving total parenteral nutrition [86]. This study signifies the absolute need for personalized medicine in diagnosis and treatment of disease.

Our biochemical pathways are complex, and an interrelationship exists between our own pathways and those of the microbes that inhabit our bodies. Subtle dysregulations can ripple through the entire system and eventually lead to single disease states, such as CVD or diabetes. Traditional diagnostic tests, based on single biomarkers, do not show the underlying shifts in metabolic pathways and often

cannot detect a problem until the disease is well established [87]. Therefore, newer assessment methods must be developed that recognize subtle, quantitative differences among humans in their metabolism and comprehensively examine metabolism to distinguish health as a continuum.

Metabolomics has challenges to address. The Human Metabolome Database lists approximately 8000 endogenous metabolites and over 6000 more that arise from pharmaceuticals, toxins and environmental pollutants and food components and additives [88]. The absolute and relative concentrations of these metabolites are a combination of intrinsic human factors such as genetics, age, reproductive status and health; extrinsic factors such as lifestyle choices, food, drink and drug intake; as well as commensal and noncommensal microbiota activity. While many of the endogenous metabolites are maintained homeostatically within serum, the majority of ingested substances move dynamically through human metabolism, altering the plasma and urinary metabolic profiles as they do. This time dependency of metabolites within individuals is also affected by intrinsic and extrinsic factors and the microbiome [89]. It is clear that if metabolomics is at all to become a paradigm shift for clinical chemistry, it must be analytical in nature; that is, researchers need to know not just the detailed image of a metabolomic fingerprint, but the actual metabolites and their concentrations so that specific metabolites and their flux can be related to specific pathways and diseases. The scope and range of metabolites within normal and pathophysiological states require that the field of metabolomics make some unifying assumptions and agree on standards for targeted metabolites and conditions of sampling in order to fully realize its potential as the next generation of clinical chemistry.

In addition to refinements for specific diagnostic tests for use in point-of-care settings and at the bedside, technological progress will be needed to miniaturize the NMR or MS instruments. Currently, the large footprints of spectroscopy equipment mean that they are best suited to hospitals and clinical laboratories. Progress in optimizing computer technology and software for interpretation of data outputs is under way. As refinement of current diagnostic tests continues and as new ones are discovered, it will be important to use untargeted approaches to observe subtle changes across the metabolome and potentially pinpoint new, unexpected biomarkers. However, once tests are developed, targeted approaches will best suit a specific test.

5. Conclusions

Unique genotypes and environments give rise to unique phenotypes, including metabolic phenotypes. One study has shown that each person has a natural metabolic phenotype that is stable and largely invariant over a period of at least 2–3 years [18]. It likely descends from systematic lifestyle and dietary habits as well as from genetics. Individual metabolic phenotypes can be regarded as images of biochemical steady states: deviations from the optimal conditions can be directly linked to a pathophysiological status or to changes in diet or environment. Metabolomics can provide accurate snapshots of an individual's nutrition and health status and thus can provide valuable feedback to health care professionals in terms of diagnosis, diet and lifestyle counseling and treatment plans. This personalized approach can lead to not only the absence of disease, but also the achievement of optimal health. Clinical metabolomics aims at evaluating and predicting health and disease risk in an individual, in a personalized manner, by investigating metabolic signatures in body fluids or tissues. Preventing metabolic illness means guiding metabolism in each individual away from existing health problems through diet and toward an optimal personal metabolic state.

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