Systems Approach to Nutrition in Pediatric and Adult Populations

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Abstract

Over the past decades, systems biology approaches have significantly contributed to the rediscovery of the intimate interactions between diet, gut microbiota, and human health. Among the new omics technologies, metabolite profiling has emerged as a robust platform to capture metabolic and nutritional requirements by enabling, in a minimally invasive fashion, the monitoring of a wide range of biochemical compounds. It provides key insights into complex metabolic phenomena as well as into differences and specificities at individual and population levels. From a nutritional perspective, our research explores how dietary macro- and micronutrients are co-metabolized by the human host and its gut microbial symbiotic partners. There are various classes of metabolites that are metabolized by the gut microbiota and seem to be involved in fundamental mammalian metabolic processes, namely short-chain fatty acids, bile acids, and amine and aromatic compounds such as indoles and phenols. By quantifying these molecular species over time, across conditions, before and after interventions, and among individuals, we generate a dynamic and mechanistic insight into human and microbial co-metabolism. Herein, we will illustrate challenges and perspectives in the context of pediatric and adult health research.

Glossary of Abbreviations
IBD: Inflammatory Bowel Disease
SCFA: Short-Chain Fatty Acids
T2D: Type 2 Diabetes

Key Words
Longitudinal
Metabonomics
Microbiota
Systems Biology

Introduction

The worldwide increase in multifactorial diseases, such as metabolic syndrome, inflammatory bowel diseases, and food allergies, has been leading to new challenges in the field of health economics.[1] Concomitant to novel clinical and biochemical analytical technologies, new scientific evidence describing underlying complexity and multifactorial origin of these disorders is a key prerequisite for comprehensive analysis and biological interpretation.[2] In this, omics technologies can contribute to creating a system view of pathogenesis by generating gene, protein, and metabolite data. The adaptation of systems biology to translational and clinical sciences has been termed network medicine and is changing the way we think about preventing, predicting, diagnosing, and treating such complex and multifactorial diseases.[3,4] It is envisioned that not only the access to unprecedented large reference databases and biobanks but also the integration and biological modelling of such data will contribute to redefining disease understanding and phenotyping. This will subsequently lead to the discovery and development of novel diagnostic and multiple pathway therapies.[3]

There is compelling evidence that lifelong health promotion and disease prevention by nutrition and lifestyle can help prevent or delay the onset of chronic diseases.[5,6] It is foreseen that the combination of personal risk factors for chronic disorders and better understanding of individual requirements for optimal lifestyle and nutrition may provide a roadmap for a healthier metabolic and clinical status.[6] Major advances in the study of host gut microbial transgenomic interactions have demonstrated that we have underestimated the extent by which the gut microbiome contributes to human health status.[7,8] From a nutritional perspective, there is major interest in better understanding how dietary macro- and micronutrients are transformed by the human body and its symbiotic gut microbial partners, and subsequently influence system and compartment molecular processes in the host.

Early Nutrition, Healthy Aging and Metabolic Diseases

Among the modern multifactorial disorders, metabolic syndrome encompasses various multifactorial metabolic abnormalities, such as glycemic control, insulin resistance, and hypertension, that associate with cardiovascular complications.[10,11] Concomitant to the obesity epidemic, maternal and childhood obesity is rising.[12] It seems well established that mother-child metabolic disease risk is driven by both genetics and early life environmental factors.[13] Childhood and parental obesity are strong predictors of later adult obesity.[14] Alteration of nutrition in childhood has been increasingly associated with later health and disease risk.[15] In particular, the rising prevalence of type 2 diabetes (T2D) and obesity in children has become an alarming problem,[16] with about one-third of children affected by transient hyperglycemia developing diabetes within one year.[17,18] It is, therefore, urgent to generate deep understanding of metabolic

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and nutritional requirements as a function of age, growth, and physiological status in childhood.[16] Such knowledge could accelerate early identification of children with T2D risk, for which the pathology could be delayed or prevented by lifestyle or medical intervention.[17]

Obesity also introduces a significant disturbance of normal growth and pubertal patterns.[12,16,19] Many other pediatric diseases are having an impact on growth and normal development during childhood and puberty and, therefore, impacting the quality of life of children and adolescents. For instance, in the context of inflammatory bowel disease (IBD), about 25% of patients develop the disease during childhood,[20] in which growth failure and delayed puberty are major complications.[21,22] Optimization of growth is, therefore, one of the critical aims in the management of pediatric IBD, especially since growth failure and delayed puberty are already present before the onset of clinical symptoms. We previously discussed how growth during childhood and adolescence occurs at different rates and is influenced by the interactions among genetic, nutritional, and environmental factors.[12,16,19]

Access to large reference data on how dietary and lifestyle habits influence metabolic functions is still lacking. Such data are required to define nutritional recommendations for macro- and micronutrients that are adapted at different stages throughout childhood in relation to growth and health state. We recently exemplified how in this context metabonomics offers a unique opportunity to monitor the metabolic status in childhood in relation to growth and disease state.[20] Urine metabolic profiles of IBD children differed significantly from healthy controls.[20] IBD children showed differences in relation to central energy metabolism, protein, and nitrogen balance, as well as to gut microbial metabolism of aromatic amino acids. The longitudinal experimental design enabled the identification of a peculiar metabolite pattern in two readouts of nitrogen metabolism, urinary urea and phenylacetylglutamine, which might enable regular assessment of the metabolism in relation to growth and disease management outcomes. Such fingerprints are means by which we might assess metabolic requirements at different stages of disease and develop adapted nutritional solutions for optimal growth catchup in children.

While susceptibility to develop metabolic diseases has increased in childhood and later in life, the overall population benefits at the same time from better nutrition, hygiene, and socioeconomic status, which all are associated with increased human longevity.[6] Such population dynamics have a major impact on health care systems, especially due to greater needs for hospitalization at advanced age.[6] Deciphering the factors that enable healthy aging and longevity, while also anticipating the consequences of increased disease risk in childhood,[6,23] has become critical.

Metabonomics is ideally positioned to capture such metabolic requirements — and in the future to better define nutritional requirements — through the simultaneous analysis of a wide range of metabolites and nutrients.[24-27] Metabolism and aging are tightly interconnected, and many metabonomic studies have revealed aging as a plastic process impacted by genetics and environment.[6,28] We recently reviewed metabonomic applications in aging,[6] where significant knowledge has been accumulated over the past decades in various model organisms including yeast, *Caenorhabditis elegans*, rodents, and the domestic dog, as well as in human aging studies.[29,30] Our previous metabonomics applications as systems biology approaches to human aging cohort revealed markedly lowered tryptophan concentrations with increasing age, with a uniquely altered pattern of glycerophospholipids and sphingolipids in the longevity phenotype of centenarians.[29,30] We discussed the association of metabolic phenotypes to oxidative and chronic inflammatory conditions of the long-living participants. We also described a profound alteration of host-gut microbial metabolic acitivites that could be related to the previously reported differences in gut microbiota structure and composition of centenarians. This was particulary exemplified through two bioactives — phenylacetylglutamine and p-Cresol sulfate — produced by gut bacteria from aromatic amino acids and further metabolized through human endogenous metabolic pathways.[29,30]

Complex remodeling of host and host-gut microbial transgenomic biochemical processes appeared to be critical for healthy growing and aging in humans, with protein and aromatic amino acid co-metabolism being a fascinating interface between diet, microbome, and host metabolic health.

Host-Microbial Metabolites in Human Nutrition Research

The introduction of metabolic profiling into nutrition research has described the depth of the involvement of the gut microbiota in the regulation of systemwide and organ-specific biochemical functions,[5,31] which molecularly connects the gut, liver, brain, and other organs.[32-34] The gut microbiota plays a key role in the development and maintenance of multifactorial and chronic disorders and may be a target for therapies.[9,35-37] While state-of-the-art microbiome profiling techniques illustrated the role of gut microbial composition in health and disease, comprehensive biochemical studies are critical to decipher microbial contribution to human metabolism and to move from statistical association to functional studies. Metabonomics has become mature enough to start providing sensitive, robust, and reproducible metabolic insights into host-microbial relationships and their influence on human health and disease. Due to the variability in space and time of host-gut microbial metabolic interactions, plus their subtle response to environmental stimuli such as diet, it is very challenging to generate holistic insights into a gut microbiome at the metabolite level. Various classes of molecules, metabolized by the gut microbiota, are involved directly and indirectly into

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metabolic and sensing processes, such as short-chain fatty acids (SCFA), bile acids, and a large range of aromatic bioactive molecules, including indoles and phenols. SCFAs result from bacterial metabolism of complex carbohydrates and also from protein and amino acids,[38-40] and include acetate, propionate, butyrate, valerate, 2-methyvalerate, and isovalerate. SCFAs have known functions in energy and signaling metabolism, for instance.[39]

Furthermore, the integrated metabolism of bile acids is a good example of the complex transgenomic biochemical interactions between mammalian host and microbial symbionts. This is particularly shown through their extensive transformation by gut microbiota and metabolic fates via enterohepatic recirculation.[41-44] In addition to their crucial role in cholesterol, lipid metabolism, drug therapeutic, toxicity, and intestinal barrier function, bile acids may have an essential role in hepato-gastrointestinal diseases, obesity, or T2D.[45-47]

Through the production of a large panel of bioactives from aromatic amino acid metabolism, bacterial metabolism also may link to several metabolic pathways of relevance for brain, metabolic, gastrointestinal, and immune functions.[6] Phenylalanine, tyrosine, and tryptophan metabolism by the intestinal microbiota, indeed, generates a variety of aromatic bioactive compounds, which enter the bloodstream to be further metabolized or detoxified by sulphate and glucuronide conjugation in the gut and liver.[6] For instance, tryptophan, an essential amino acid metabolized in brain, liver, the central nervous system, and other peripheral tissues, is central for mood, cognition, and immune metabolism.[48] Interestingly, tryptophan metabolism is influenced by dietary intake and gastrointestinal ecosystem, with about 6% of dietary tryptophan being metabolized by the gut microbiota.

Cumulative scientific evidence demonstrated the extent by which gut microbiota affects not only the diversity but also the bioavailability of phenol- and indole-containing compounds in circulation in mammals. Through their peculiar metabolism of aromatic amino acids, gut microbial metabolism may influence the availability of essential precursors to host endogenous processes. This is exemplified through circulating levels of serotonin three times higher in conventional animals compared to germ-free animals.[49] Furthermore, indoles are potent signaling molecules with either beneficial (antioxidant) or harmful (uremic toxins) effects to the host.[6] Their effects are quite broad from modulating the expression of inflammatory-related genes and epithelial cell barrier function[50] to various regulatory and signaling proteins.[51] Indoles are well-characterized endogenous ligands of the transcription factor aryl hydrocarbon receptor, which link their metabolism to cardiotoxicity, vascular inflammation, oxidative, and immune-modulatory processes.[51]

Phenylalanine and tyrosine co-metabolism is another example of complex transgenomic biochemical interactions. Various organic acids containing phenyl groups can be produced from these precursors in the presence of specific gut microbes.[49] As an example, p-Cresol, a bacterial product of tyrosine metabolism, and its hepatic byproducts through phase II metabolism — p-Cresyl-sulfate — are abundant in urine[52-54] and have been identified in several metabonomic studies as a key readout for various clinical endpoints.[55-58] Preclinical investigations demonstrated how p-Cresol metabolites may modulate host metabolic functions, including endothelial permeability,[59] glucose,[60] and dopamine metabolism.[61]

In the near future, new high-throughput analytical methods will enable rapid measurement of gut microbial metabolites in large populations, which will generate unprecedented reference data to be translated for medical and nutritional applications.[73] Some perspectives were recently illustrated through mathematical modeling of the human gut microbiome at genome scale to decipher microbe-microbe, diet-microbe and microbe-host interactions.[74,75] Such applications demonstrate that it is now possible in human studies to model the influence of gut microbial metabolism on fecal and serum amino acid levels in response to dietary intervention.[74,75]

Conclusions

Throughout the life stages, physiological processes involved in childhood growth and development, as well as during aging, involve multiple genetic, biochemical, and metabolic processes. The establishment of novel systems biology will be essential in (re-)defining metabolic and nutritional requirements throughout these life stages. Applications of metabolite profiling technologies to large and longitudinal cohort studies will be essential to understand biochemical and physiological processes that contribute to growth and development as well as physiological decline during aging. We also envisioned that deciphering the interactions between human cells and intestinal microbiome will foster the identification of new molecular targets and the exploitation of microbiota as a therapeutic target.[9] In this, microbiota-derived metabolites can provide a molecular signature of such interactions with potential health-associated outcomes.

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