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Importance of Nutrients and Nutrient Metabolism on Human Health

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Nutrition transition, which includes a change from consumption of traditional to modern diets that feature high-energy density and low nutrient diversity, is associated with acquired metabolic syndromes. The human diet is comprised of diverse components which include both nutrients, supplying the raw materials that drive multiple metabolic processes in every cell of the body, and non-nutrients. These components and their metabolites can also regulate gene expression and cellular function via a variety of mechanisms. Some of these components are beneficial while others have toxic effects. Studies have found that persistent disturbance of nutrient metabolism and/or energy homeostasis, caused by either nutrient deficiency or excess, induces cellular stress leading to metabolic dysregulation and tissue damage, and eventually to development of acquired metabolic syndromes. It is now evident that metabolism is influenced by extrinsic factors (*e.g.*, food, xenobiotics, environment), intrinsic factors (*e.g.*, sex, age, gene variations) as well as host/microbiota interaction, that together modify the risk for developing various acquired metabolic diseases. It is also becoming apparent that intake of diets with low-energy density but high in nutrient diversity may be the key to promoting and maintaining optimal health.

INTRODUCTION

Over the last several decades, many jurisdictions around the world have witnessed the increasing prevalence of acquired metabolic syndromes, in particular obesity, diabetes, fatty liver disease and cardiovascular diseases [1-4]. In recent years, the upward trend is especially striking in developing countries where changes in diets and lifestyle accompany modernization [1,5]. To counter the increasing public health complications caused by changing nutrition practices, health organizations have provided dietary recommendations [6]. Whereas past interventions designed to address cases of single nutrient deficiencies have achieved clear indicators of success [7], intervention trials that target a single class of nutrients to manage the emergence of metabolic diseases in the general population have not produced definitive results [8,9]. It is increasingly being realized that comprehensive analysis of what is being consumed together with the eating pattern, rather than focusing on single nutrients,

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may be more informative in formulating effective dietary recommendations.

Recent advances in high-throughput analysis have assisted in a better understanding of metabolism and revealed the active role of nutrients and their metabolites in regulating gene expression and cellular function. Nutrients and their metabolites not only serve as building blocks of cellular structures and as fuel sources, but also serve as direct modifiers of protein function, potent signaling molecules as well as inducers and repressors of gene expression. Many of them participate in regulating gene expression by directly modulating the activities of transcription factors and by moderating the changes in epigenetic markings in the genome. One view that is emerging is that optimal cellular homeostasis is crucial for maintaining health and avoiding diseases caused by nutrient deficiency or excess. In addition, intrinsic factors (*e.g.*, sex, age, gene variations), extrinsic factors (*e.g.*, food, xenobiotics, environment) as well as host/microbiota interaction can influence the assimilation, transformation, and action of both nutrients and non-nutrient components of food. This review considers the importance of nutrient diversity and energy density on cellular metabolism in health and disease (Figure 1).

QUALITY OF NUTRITION

Single nutrient interventions such as fortification of milk with vitamin D, cereal with iron, and table salt with iodine were effective in treating the corresponding nutrient deficiencies [10]. However, when applied to acquired metabolic syndromes that prevail in modern societies, the same approach has yielded inconclusive results [11,12]. For example, decreasing dietary intakes of saturated fatty acid or cholesterol, and increasing the intake of omega-3 polyunsaturated fatty acids do not appear to be effective in reducing the risk of cardiovascular diseases [9,13,14]. The importance of the entire diet that is consumed as a regular practice is being recognized, and an increasing number of studies are analyzing dietary pattern to identify possible causes of under- and over-nutrition. By definition, dietary pattern characterizes the overall diet by the quantities, the proportion, and the variety of foods and beverage as well as the frequency of consumption [15]. The Mediterranean pattern and Western-style pattern are two commonly practiced dietary patterns. The Mediterranean diet contains a high proportion of fruits and vegetables, legumes, whole grains, fish, and poultry with an emphasis on monounsaturated fats and antioxidants, whereas the Western-style diet is generally characterized by energy-dense foods like butter, high-fat dairy products, refined grains, as well as processed and red meat, leaving less space for other nutrients especially those coming from fruits and vegetables. Epidemiological studies have found that the Mediterranean dietary pattern has preventive and protective effects against cardiovascular diseases [16,17], whereas the Western-style dietary pattern is positively associated with dyslipidemia, obesity, hypertension, atherosclerosis, and diabetes [18,19].

Nutrition transition refers to the shift of diet from traditional to modern along with an increase in sedentary behavior, that occur in conjunction with modernization. The concept of nutrition transition was initially proposed by Popkin [20,21] to demonstrate how economic, demographic, and epidemiological changes interact with shifts in dietary consumption and energy expenditure. Interestingly, some countries in East Asia have lower prevalence of certain acquired metabolic syndromes compared to other societies at comparable stages of nutrition transition [2,5,22]. This might be partially due to retention of traditional dietary patterns, which promote consumption of foods with a wider array of nutrients and lower energy density [23-25]. However, the reasons underlying the discrepancy are complex, and extend beyond the chemical composition of food to include social and economic issues. Nevertheless, there is evidence supporting the idea that calorie restriction is beneficial for longevity [26-28], providing support for the potential benefit of low-energy density diets (Figure 1A).

The prevailing global increase in the development of acquired metabolic syndromes is associated with nutrition transition [29,30]. One proposed concept that potentially explains the pathogenesis of these syndromes stems from persistent modification of cellular function in response to stress in the endoplasmic reticulum, mitochondria, and other organelles that make up the cellular reticular network [31]. Both nutrient deficiency (undernutrition) and nutrient excess (over-nutrition) cause the loss of nutrient/energy homeostasis and thus trigger cellular stress. Coping response mechanisms, such as the unfolded protein response mechanism [31-33], are activated to resolve stress. In the case of a maladaptive response, programmed cell death is activated to remove malfunctioning cells. On the other hand, persistent adjustment of cellular functions enables cells to cope even with continued exposure to stress inducers. Stress coping response mechanisms initially promote adaptive strategies to recover homeostasis in the short term but become pathogenic in the long term due to long-term modification of cellular functions.

FOOD COMPONENTS

Food is a complex combination of numerous components which can be classified into nutrients and non-nutrients. Nutrients have been traditionally classified as macronutrients and micronutrients. Plants and animals do not have identical nutrient requirements and produce nutrient metabolites that may not be common to each other.
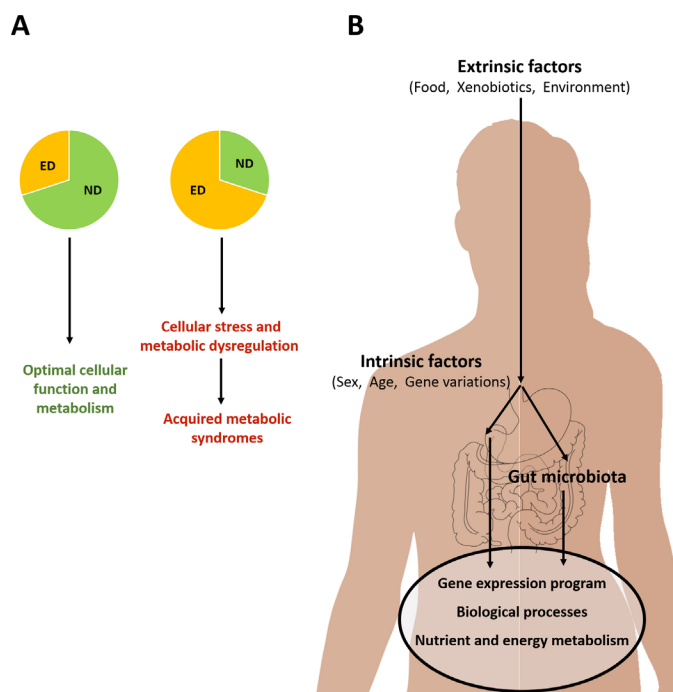
Figure 1. **Factors that influence human health**. **A**. Relationship of nutrient diversity (ND) and energy density (ED) in equivalent portion sizes, and their impact on cellular metabolism. **B**. Extrinsic factors (*e.g.*, food, xenobiotics, environment), intrinsic factors (*e.g.*, sex, gene variations, age), and host-microbiota interaction work together to modulate gene expression program, biological processes, and nutrient and energy metabolism.

Micronutrients, which include vitamins and minerals, are needed in only small amounts, and are required for the proper function of important proteins and enzymes. Macronutrients, which include carbohydrates, proteins, and fats, are typically needed in large amounts. The benefits of consuming macronutrients are self-evident since their subunits serve as building blocks of cellular structures and as energy substrates in all organisms. Some species are unable to synthesize key metabolites needed for survival, and thus must obtain these from other species. These essential metabolites, along with minerals, make up a class of substances referred to as essential nutrients. Non-nutrient components of food are those that cannot be categorized as either macronutrients or micronutrients. These substances include both natural and synthetic compounds. They can be beneficial (*e.g.* fiber, and some polyphenolic compounds produced by plants), non-beneficial (*e.g.* many food additives, and preservatives) or even toxic (*e.g.* xenobiotics, and antibiotics, also some plant-derived polyphenolic compounds) [34,35]. It has become evident that both nutrients and non-nutrients, as well as their metabolites, have the capacity to modulate gene expression, protein function and epigenome [36-38].

The potential of macronutrients and their metabolites to regulate metabolic function is typically taken for granted. For example, the monosaccharide fructose

is commonly used as a sweetener in commercially prepared foods and is present in these foods at exceedingly high amounts compared to natural foods [39]. Fructose is known to stimulate *de novo* lipid synthesis in the liver and to induce endoplasmic reticulum stress in many cell types [40,41]. In general, excess glucose and fructose induce cellular stress which leads to the development of insulin resistance and fatty liver disease [40,42,43]. Certain amino acids have been shown to act as signaling molecules to regulate cellular growth and proliferation via mTOR (mechanistic target of rapamycin) [44,45], whose function has been implicated in many human diseases [46]. Some fatty acids from fats and oils serve as ligands for G protein-coupled receptors as well as for transcription factors belonging to the nuclear receptor family of transcription factors [47,48], and therefore regulate cellular processes and gene expression [49]. Saturated fatty acids have long been the focus of investigation as high intake of saturated fats was considered to be a risk factor for cardiovascular diseases [50], however subsequent studies have not provided strong evidence for causality [9]. This may be partly attributable to the wide range of biological activities associated with different fatty acids species [51]. Palmitic acid, a fatty acid species that is enriched in the Western-style diet, is a potent inducer of endoplasmic reticulum stress whereas oleic acid, a fatty acid

prominent in the Mediterranean diet, has been shown to inhibit endoplasmic reticulum stress [52,53]. Importantly, the surplus of nutrients and energy induce endoplasmic reticulum stress and inflammatory responses that lead to systemic metabolic dysregulation [31,32].

Many metabolic diseases caused by micronutrient deficiencies can be corrected by restoring the missing micronutrients in the diet [54,55]. One critical aspect of micronutrient supplementation applied to the general population is overdose. Some of these compounds are potent modulators of nuclear receptors and have serious impacts on the activities of multiple metabolic pathways. For example, deficiency of vitamin A can lead to blindness while its excess is teratogenic. Vitamin D also modulates the expression of many genes that participate in many pathways [56], and its deficiency causes rickets. However, it is not yet known if it is possible to overdose with this micronutrient. Excessive dietary intake of minerals can be equally deleterious, as exemplified by diet-induced hypertension due to high intake of sodium [57].

Other metabolites produced by the mammalian metabolic machinery also play critical roles in metabolism. For example, cholesterol serves as a membrane component, signaling molecule, and precursor for the synthesis of steroid hormones and bile acids [58]. Bile acids aid in the absorption of dietary fats and lipid-soluble compounds, and also act as signaling molecules modulating macronutrient and energy metabolism, inflammatory responses, and detoxification through intracellular ligand-activated nuclear receptors [59]. Gut bacteria are capable of metabolizing bile acids and one of the products is a secondary bile acid referred to as ursodeoxycholic acid. It is of interest to note that this bile acid and its taurine-conjugated derivative can alleviate endoplasmic reticulum stress by promoting proteostasis [60], and has been shown to be effective in preventing cardiac fibrosis [61,62].

The non-nutrient components of food can be beneficial or non-beneficial. Beneficial ones include fiber and certain types of plant polyphenolic compounds. Dietary fiber, derived from plant-based foods, is not an effective nutrient for humans, but serves as a nutrient for gut microflora. Some of the products generated from dietary fiber include short chain fatty acids (*e.g.*, butyric and propionic acids) that are absorbed in the lower gut and serve as both energy substrates and regulators of host metabolism [63,64]. Plant polyphenolic compounds have been popularized as anti-oxidants. However, there are numerous polyphenolic compounds present in plants, and these compounds likely have a wide range of biological activities and effects on human metabolism [65,66]. A polyphenolic-rich extract prepared from potatoes exhibits beneficial activity by attenuating weight gain in mice fed with obesity-inducing high fat diet [67]. There is also emerging evidence for the modulating effect of polyphenols on the composition and metabolic activity of gut microbiota that provides potential benefits to the host [68]. Not all polyphenolic compounds are beneficial, as some compounds such as caffeic acid and genistein may be carcinogenic or genotoxic at high dosage [34,69,70]. It is commonly assumed that synthetic food additives (colorants, preservatives, sweeteners) do not have effects on metabolism, but this assumption should be tested regularly to ensure food safety. Other xenobiotics (*e.g.* pollutants, drugs, and agricultural chemicals) that find their way into the food supply can influence human health directly, by disrupting normal metabolic processes, or indirectly, by influencing the composition of the gut microbiota [71]. All food components likely work together to drive metabolic processes in every cell of the body.

FACTORS THAT INFLUENCE HUMAN NUTRITION

It is now evident that both extrinsic factors (such as food, xenobiotics, environment) and intrinsic factors (such as sex, age, gene variations), separately and cooperatively, influence nutrient metabolism and the risk for developing various metabolic diseases (Figure 1B). Extrinsic factors are important in dictating the efficiency of nutrient metabolism and health outcomes, including physical cues such as photoperiod and temperature. For example, the alternating light/dark photoperiod of the day-night cycles is important in setting endogenous circadian rhythms, which in turn are intimately linked to the regulation of metabolic activity [72]. Detrimental environments, which include situations that induce the release of stress hormones, can impair the ability of the body to sense and respond to metabolic challenges [73-75]. Extrinsic factors also promote alterations of the epigenome which can have long-lasting impacts on nutrient and energy metabolism and contribute to the development of metabolic disorders in organs like the heart (*e.g.* coronary heart disease) and the brain (*e.g.*, Alzheimer's disease) [76-78].

Similarly, intrinsic factors such as gene variations, sex, and age, influence the efficiency of nutrient metabolism (Figure 1B). Genetic variations impact on the efficacy of metabolic pathways by affecting the function and specific activities of membrane transporters, receptors, signaling proteins, enzymes, carrier proteins, transcription factors, and other proteins involved in the transport, sensing and processing of specific nutrients [79]. For example, single nucleotide polymorphisms in genes encoding taste receptors influence food preferences [80]. Variations in NPC1L1 cholesterol transporter influence dietary cholesterol absorption [81,82]. Sex and aging determine the biological context and represent important modifiers of metabolic efficiency. Males and females have distinct
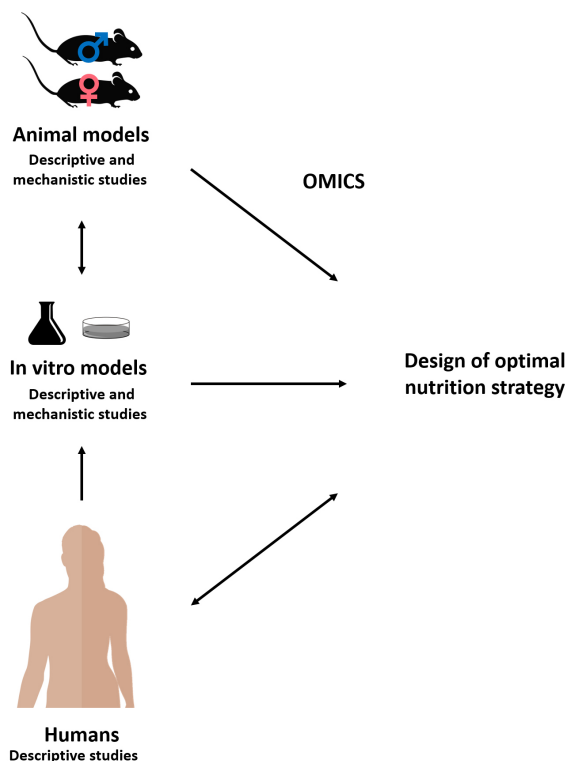
Figure 2. **Modern approaches used in the study of nutrition**. Descriptive data obtained by Omics technologies from both human studies and animal models to guide mechanistic studies in *in vitro* and cell models. These approaches collectively provide information for the design of interventions for promoting optimal nutrition.

features in terms of metabolic profiles, gene expression programs, and susceptibility to diseases [83-87]. Aging is associated with the loss of metabolic efficiency caused by deterioration of cellular and genetic components resulting from chemical damage accumulated through life stages. At the cellular level, aging is associated with gradual changes in cellular processes designed to maintain homeostasis. However, these adaptive changes that alter cellular metabolism may contribute towards the loss of metabolic efficiency at the organismal level [31]. Remodeling of the epigenome through life stages may also influence disease susceptibility in elderly individuals [37].

The gut microbiota represents an important interaction nexus for extrinsic and intrinsic factors that influence the metabolism of nutrients (Figure 1). This enormous ecosystem has gained increased attention in recent years for its role in health and disease. Due to its location, the gut microbiota is exposed not only to the same extrinsic factors experienced by the host but also the metabolites and products produced by the host, such as bile acids, digestive enzymes, and other substances excreted into the gut. Males and females have distinct microbiomes, as do young and old individuals [62,88,89]. Recent studies show that the composition of the gut microbiota can have dramatic effects on the phenotype of the host.

For example, transplantation of fecal microbiota from a twin pair discordant for obesity into germ-free mice reproduces the obese/lean phenotypes of the donors in their respective recipients [90]. Gut microbiota taken from children suffering from kwashiorkor can induce significant weight loss when transplanted into germ-free recipient mice [91]. Moreover, the gut microbiota may be capable of altering the susceptibility of its host to metabolic diseases, by transforming non-nutrient components of food into useful nutrients for the host. Short-chain fatty acids produced from breakdown of dietary fibers can influence the expression of genes involved in proliferation and differentiation of mammalian colonic epithelial cells. They also serve as energy substrate elsewhere in the host [63,92]. Other non-nutrient components of food, such as artificial sweeteners which are deemed safe for human consumption, have been shown to induce dysbiosis in gut microbiota, transforming it into a pathogenic profile [35]. It was recently suggested that even the use of natural substances, such as trehalose, as routine food additives could have deadly consequences for public health [93]. The emergence of a highly infectious strain of *Clostridium difficile* is coincident with the introduction of trehalose into prepared foods, and it is suggested that this compound had permitted the selection and expansion of pathogenic

strains by providing a carbon source and energy substrate not normally used by the non-pathogenic strain of this bacterium [35]. These examples illustrate the importance and interaction of extrinsic and intrinsic factors in modulating and integrating nutrient metabolism, and in determining the nutritional status of the organism.

TECHNOLOGIES USED IN THE STUDY OF METABOLISM AND NUTRITION

Over the last few decades, the study of metabolism and nutrition has gradually increased in scope in its mission to find ways of alleviating hunger and improving nutrition and health status. With better understanding of cellular and whole-body metabolism, it has become apparent that optimal nutrition is not simply a case of energy adequacy but also that of nutrient diversity (Figure 1A). To address the complicated metabolic disorders that stem from over-nutrition and sub-optimal nutrition, it is necessary to apply multipronged approaches using a variety of experimental systems targeted at various levels of biological organization (Figure 2).

Animals and humans do not share identical nutrient requirements, but animal models have nonetheless been indispensable in elucidating the processes involved in the metabolism of nutrients. Transgenic and targeted gene disruption technologies applied to mice have greatly contributed to understanding the role of specific genes and their associated polymorphisms in dictating the efficiency of nutrient metabolism. It has been possible to recapitulate human metabolic diseases in these models, as well as to allow the study of human genes *in vivo* [94-97]. The recent advent of CRISPR/Cas9-mediated gene editing will further simplify the creation of new animal models [98]. With better awareness of the impact of sex differences [85], future studies can be designed to collect information from both sexes in regard to responses to specific nutritional interventions. Cell culture models have served as useful platforms for elucidating the molecular mechanisms that underlie nutrient metabolism. The use of cells from both experimental animals and human donors can also highlight species-specific differences that impact on nutrition. These models can help to provide insights into descriptive data generated by human intervention trials. It will be important to rigorously design these intervention trials so that these studies generate high quality data that are needed for reliable interpretations.

Omics technologies (genomics, transcriptomics, proteomics, and metabolomics) provide a diverse and rich source of descriptive information needed for the detailed surveillance of nutrient metabolism in humans and experimental models [99]. Fortunately, suites of mature bioinformatics tools and the necessary computing power are now available to decipher these data and infer relationships among genomes, metabolic processes, and cellular functions that are relevant to health and disease [88,100-102]. A coordinated strategy may be useful in integrating the mechanistic and descriptive information drawn from various sources to generate the knowledge that can ultimately be used to formulate useful recommendations for optimal human nutrition and health.

SUMMARY

Nutrients have been commonly regarded as nourishment, providing raw materials needed for cells growth and proliferation, and fuel for powering cellular metabolism. However, in addition to these roles, it is evident that nutrients and their metabolites are also active in the facilitation, regulation, and coordination of the vast number of cellular processes that operate to maintain cellular homeostasis. Effective cellular function depends on context, such as sex and age, as well as ideal supply of necessary nutrients. The processed foods that are prominent in the Western-style dietary pattern may be the important factor responsible for the rise of acquired metabolic syndromes as seen in developed societies. The long-term consumption of these foods, which typically have poor nutrient diversity and excessive energy content, lead to deficiencies in key nutrients and excess fuel substrates that likely trigger the loss of cellular nutrient/energy homeostasis. Due to the continued exposure of cells to stressors, the metabolic changes at the cellular level intended initially as adaptive strategies, persist and ultimately become the driver of metabolic dysfunction at the organismal level. Recent advances in high-throughput analyses, creation of animal models of human metabolic diseases and bioinformatic tools hold promise for accelerating the process of formulating more effective nutritional recommendations. In the meantime, consumption of foods with low-energy density and high nutrient diversity seems to be a prudent approach for minimizing cellular stress and the promotion of optimal cellular function and health.

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