Energy intake, metabolic homeostasis, and human health

Guangchang Pang *, Junbo Xie, Qingsen Chen, Zhihe Hu

Tianjin Key Laboratory of Food Biotechnology, College of Biotechnology and Food Science, Tianjin University of Commerce, Tianjin 300134, China

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Abstract

The energy substances (mainly carbohydrates and fats) are the basis and guarantee of life activity, especially the oxidative phosphorylation for energy supply. However, excessive absorption and accumulation of these substances can lead to metabolic diseases such as obesity, hyperlipidemia, diabetes, and cancers. A large amount of studies demonstrate that G protein-coupled receptors (GPCRs) play a key role in identification and absorption of energy substances, and the signaling network of nerves, immune, and endocrine regulates their storage and utilization. The gastrointestinal mucus layer not only identifies these substances through identification in diet components but also transfers immune, metabolic, and endocrine signals of hormones, cytokines, and chemokines by promoting interactions between receptors and ligands. These signaling molecules are transferred to corresponding organs, tissues, and cells by the circulatory system, and cell activity is regulated by amplifying of cell signals that constitute the wireless communication network among cells in the body. Absorption, accumulation, and utilization of energy substances in the body obey the law of energy conservation. Energy is stored in the form of fat, and meets the demand of body via two coupled mechanisms: catabolism and oxidative phosphorylation. Under normal physiological conditions, fat consumption involves ketone body metabolism through the circulatory system and glucose consumption requires blood lactic acid cycle. Accumulation of excessive energy leads to the abnormal activation of mammalian target of rapamycin (mTOR), thus promoting the excretion of glucose or glycogen in the form of blood glucose and urine glucose. Alternatively, the body cancels the intercellular contact inhibition and promotes cell proliferation to induce carcinogenesis, which can induce the consumption of large amounts of glucose. Intercellular communication is performed by signaling molecules via sensing, absorption, accumulation, and utilization of energy substances, and anabolism and catabolism are controlled by the central metabolic pathway. Therefore, slower catabolism will result in longer life expectancy, whereas faster catabolism results in shorter life expectancy. Energy substances in diet influence the balance between energy and metabolism in the body through the sensing function of the gastrointestinal system at two levels: cellular communication network and metabolic network. The present review of studies aims to strengthen our knowledge on cellular communication and metabolic networks to offer a dietary guidance on the metabolism and communication role of various foods.

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1. Introduction

Basic nutrients, such as carbohydrates, fats, and proteins, are the foundation of all life activities. They constitute the carbon skeleton (intermediate metabolites) of various functional molecules, and provide energy through oxidative decomposition. Traditionally, the main aim of nutrition is prevent and treat nutritional deficiencies. However, when nutrition is adequate or excessive, the body faces the problems of quantitative control of the nutrients absorption and storage. Overnutrition, especially absorption and storage of energy, can not only affect health but also cause many diseases such as diabetes, cardiovascular diseases, obesity, hypertension, and hyperlipidemia. Further, overnutrition reduces reproductive capacity and promotes the development of various cancers that will seriously affect quality of life, survival, and reproduction in human beings.

Because of overnutrition, nutritionology based on nutritional requirements cannot make recommendations for nutrient intake
in daily life because nutrient absorption, energy storage, and oxidative energy supply control vary from person to person. Even during evolution, nutritional experience seems to be recorded in the nucleosomes and DNA, which involves all aspects of nutrient sensing, cell communication, metabolic regulation, gene expression, and epigenetic modifications. However, food intake is a fundamental activity of the human body and is a source of energy. This study reviews the relationship among energy absorption, metabolism, and human health to systematically analyze and discuss signaling processes, metabolic control mechanisms, and corresponding diseases due to overnutrition. This review also highlights the key problems that need to be resolved and puts forth views for future development.

2. Sensing and quantification of energy substances

In 2012, the Nobel Prize in Chemistry was awarded to two American scientists Robert J. Lefkowitz and Brian K. Kobilka for their outstanding contribution to our understanding of G protein-coupled receptors (GPCRs). Absorption and quantification of nutrients mainly occurs via the sensing function of GPCRs. The GPCR superfamily includes many receptors that sense all nutritional components, especially energy substances. GPCRs are highly conserved molecules from microorganisms to humans. GPCRs are coupled to G protein cascade activation and signal transduction to transfer structural and functional information of nutrients, non-nutrients, and food safety to the body by taste and smell and the gastrointestinal (GI) system, thus forming the physiological basis of nutrient absorption and quantitative control, safety and defense, and stress and relaxation [1].

Due to their transmission function of smell, taste, light, sound, signal as well as immunity, hormone, defense and other physiological functions, the GPCR family members are the most important screening target of medicine, functional foods, and food additives. Previous studies have described that GPCRs are involved in multiple signaling pathways by coupling with G proteins and perform various physiological and pathological functions by controlling the signaling pathway of mammalian target of rapamycin (mTOR). MTOR not only controls synthesis and catabolism but also controls energy operation, substance distribution, endocrine function, storage, energy oxidation, cell cycle, growth, development, differentiation, reproduction, apoptosis, autophagy, carcinogenesis, and lifespan. MTOR is an important molecule that senses, quantifies, and responds to basic nutrients such as glucose, amino acids, and fatty acids [2].

2.1. Sensing effect of the GI receptor system on nutrition

Higher animals successively have various receptor systems that can recognize sense, quantify, and transfer various signals to the body to initiate ordered physiological activities sequentially from the first exposure to foods to absorption. The receptor system is classified into two types. The first type of receptors include visual, auditory, olfactory, and taste receptors and the stomach, which quickly respond and transfer neural and endocrine signals to control appetite and to select foods. The second type includes the intestinal system that identifies the functions and molecular structures of different nutritional components in foods and delivers biochemical signals involving various cytokines, chemokines, and hormones to recognize the quality and quantity of ingredients in foods [3]. Several investigations have proven that the body uses this complex nutritional or non-nutritional sensing system to control food choice, food intake, digestion, and absorption qualitatively and quantitatively, indicating that this sensing system allows adaptation to different nutritional environments. Inappropriate control results in nutritional defects or overnutrition, subsequently leading to various diseases.

2.1.1. Taste sense: quantitative detection of nutrition in the human body

The taste sense can identify nutrient categories and determines their absorption. Humans have five taste senses, namely, sweet, salty, delicious, bitter, and sour. Sweet foods imply carbohydrates and energy substances; salty foods include Na⁺ and other salts required for life activities; delicious foods include proteins, amino acids, and nucleotides; bitter foods include bitter-tasting substances, including convergent and antinutrient substances; and sour foods include substances that undergo anaerobic fermentation to produce short-chain fatty acids (SCFAs). Because fat is associated with fragrance and is an important energy substance, some researchers have suggested the flavor of fat as the sixth taste sense, i.e., fragrance [4]. Throughout evolution, this receptor sensing system has ensured abundant supply and proper storage of nutrients, thus preventing unfavorable nutrient uptake or unsafe food intake.

2.1.2. Taste bud cells and their sensing functions

Taste receptor cells (TRCs) in taste buds interact with each other and transmit electrochemical signals that are amplified by the G protein signaling system. When these electrochemical signals reach a threshold of nerve stimulation, TRCs transfer signals to specific taste perception areas in the brain through afferent nerves. TRCs are classified into four types according to their morphological characteristics [5]. Type I glia-like cells transmit signals for saltiness while type II cells transmit signals for sweetness, deliciousness, and bitterness. Type III cells sense sours while type IV cells are stem/progenitor cells of taste. Members of TAS1R family are heterodimers that directly sense sweetness (TAS1R2–TAS1R3) and deliciousness (TAS1R1–TAS1R3). TAS2R receptor family includes >25 members that directly sense bitterness [6]. Fat-sensing receptors such as FFAR1 and GPR120 are expressed by type I and II cells, respectively [7]. Taste receptors are not only present in cells of the taste buds but also in cells of the GI tract, respiratory tract, pancreas, brain, and other organs. The complex of tastants such as sweetness, fatty, bitter, and delicious substances initiate the release of second messengers, which then initiate cascade amplification to accelerate the release of peptides or neurotransmitters (electrical signals). Some peptides contribute to taste sensing; for example, α-peptides can not only recognize bitterness and sweetness but also partially recognize fat flavor [8]. These α-peptides affect cAMP and cGMP and activate phosphatase Cβ2 (PLCβ2) through the flavor peptide βγ (β3γ13) to transfer quantitative signals, which can induce the IP3-mediated
release of Ca\(^{2+}\) in cells, and the transient activation and the membrane polarization of receptor potential-cation channel subfamily M member 5 (TRPM5), as well as can generate action potentials and accelerate ATP release and then quantitatively activate purinergic receptors to sense by afferent nerves, thus realizing the sensing and quantification of taste and smell sense in brain.

2.1.3. Nutrient sensing, quantification, and appetite control in the digestive tract

Release of hormones in the intestinal tract involves absorption of foods and depends on the nutrition level and state of foods, suggesting that the intestinal tract performs chemical sensing and quantification of nutrients [9]. Similar to the taste buds, GPCRs in the intestinal tract sense sweetness, bitterness, deliciousness, and fat flavor. GPCRs expressed by mucosal and endocrine cells of the digestive tract interact with other chemical signals and release hormone signals, thus quantitatively controlling absorption, storage, and balance of nutrients in the body. In a healthy state, these nutrient-sensing receptors inhibit excessive nutrient intake and absorption. However, disruption of this function results in nutritional defects and causes diseases such as obesity, diabetes, and cancers because of overnutrition.

2.2. Nutrient-sensing cells and their counting system and molecular mechanisms in digestive tract

2.2.1. Sensing function of the GI tract

GI tract is the most important nutrient-sensing system in the human body. The GI tract responds to several signals in the intestinal lumen, including nutrients, non-nutrients, various physical factors, and microorganisms. Studies have shown that the sensing system in the taste buds sends signals to the entire GI tract to initiate the absorption and digestion of nutrients in foods. Molecular sensing of GI cells plays an important role in initiating hormonal and neural responses, ion transportation, regulation, physical exercise, appetite, insulin secretion, and other physiological processes [10]. Sensing cells are directly in contact with the lumen components and sense signals through vagal afferent nerves in the lamina propria. They do not enter the epithelial layer, indicating that sensing of nutrients send signals to neurons indirectly through the epithelial layer. Signal-transmitting cells in the intestinal system include intestinal cells, brush border cells, and enteroendocrine cells (EECs) [11].

Nutrients are sensed by different GPCRs, are transported actively by the sensing cells, and are quantified by energy consumption. The underlying molecular mechanism is as follows: GPCRs induce G protein cascade to release the second messenger, thus driving the switching of sodium pump and calcium ion channel; promoting the release of multiple regulatory peptides in GI tract; transmitting signals to the central nervous system; and controlling nutrient absorption, metabolism, and appetite by changing intercellular communication network.

2.2.2. Quantitative mechanism of sensing signals

Intestinal cells are nutrient-absorbing cells. These cells contain many microvilli that greatly increase the contact area for nutrients, and various carriers that absorb glucose, fatty acids, and amino acids from the intracavity. Brush border cells are independent sensing cells [12]. In most regions of the GI tract, these cells express taste signal-transmitting molecules such as α-monosodium glutamate, α-transducin, and TRPM5 [13]. Expression of these molecules is higher in the region of the GI tract associated with digestion and absorption [14]. EECs account for <1% of the epithelial cells. However, these cells form the largest endocrine system in the body. More than 20 different types of EECs produce and secrete various hormones such as gastrin (secreted by G cells), ghrelin (secreted by P or X/A cells), somatostatin (secreted by D cells), cholecystokinin (CCK; secreted by type-I cells), 5-HT (secreted by enterochromaffin cells), glucose-dependent insulinotropic peptide (GIP; secreted by K cells), and glucagon-like peptide (GLP) and peptide YY (PYY; secreted by L cells). EECs are of two types: (1) “open cells” with microvilli, which directly sense various nutrients in the intestinal cavity, release hormones into the circulatory system, and activate afferent nerves and (2) “closed cells,” which play an indirect role in neural pathway or have effects through transmission of the signals by the circulatory system. Various appetite-restricting hormones (including GLP-1, tyrosine, PYY3-36, and CCK) and appetite-enhancing hormones (ghrelin) are released by the GI mucosa, which play an important role in controlling food intake [15]. For example, levels of GLP-1, PYY, and CCK in the plasma increase after a meal while those of ghrelin decrease, which is obviously relevant to the control of calorie depending on nutrition [16].

2.3. Major sensing receptors of energy substances and their distribution

Because energy substances are required for many important life activities in the human body, they should be supplied at appropriate intervals and stored appropriately. Senses such as sweetness, deliciousness, and fragrance are used as a “reward,” which constitutes the major driving force of food intake. Previous studies have shown that sensing receptors of energy substances are distributed not only in the olfactory and gustatory systems but also in the intestinal system.

2.3.1. Sweetness receptors and their distribution

Compared to intravenous infusion, oral administration of glucose promotes insulin secretion because of the higher secretion of GLP-1 and GIP. Sweetness receptors are present in the brush border cells, L cells, and X/A cells of the endocrine system [17] but not in the stomach, as observed in some previous studies. Both in vitro and in vivo studies have shown that α-monosodium glutamate interacts with complexes of sweet taste receptors to control the release of antidiabetic hormones and absorption and storage of nutrients in the body [18].

2.3.2. Deliciousness receptors and their distribution

Deliciousness receptors are made of taste receptor heterodimers such as TAS1R1–TAS1R3 [19] and are expressed by the brush border cells, endocrine L cells, and X/A cells in the digestive tract, which also belong to the family of metabotropic
2.3.3. Fragrance receptors (fat-sensing receptors)

In the GI tract, fat is broken down into free fatty acids by lipase. Medium-chain fatty acids (MCFAs) (6–12 C) have passive diffusion and absorption capacity in the intestinal tract. Long-chain fatty acids (LCFAs) are transported by CD36, namely, fatty acid transporter protein 4. Monocarboxylate transporter isoform-1 is involved in the absorption of SCFAs in the colon. Fatty acid absorption involves nuclear receptors such as peroxisome proliferator-activated receptors (PPARs); however, they are also sensed by GPCRs. FFAR1 (GPR40) is activated by MCFAs and LCFAs while FFAR1 is expressed in many endocrine cells but not D cells [30]. GPR120 is also activated by MCFAs and LCFAs and promotes the secretion of GLP-1, CCK, and insulin in STC-1 cells stimulated by FFAs [31]. GPR120 is expressed by ghrelin-secreting cells in the duodenum of mice. Oral administration of GPR120 antagonists such as grifolic acid increases the secretion of ghrelin. GPR120 antagonists not only improve insulin sensitivity but also reduce fat inflammation. SCFAs cannot be used as carbon source, but are sensed by free fatty acid receptors 2 and 3 (FFAR2 [GPR43] and FFAR3 [GPR41], respectively) [32], which induce the secretion of GLP-1 and PYY [33] and mediate cellular immunological regulation. GPR119 is expressed in L cells and GLUTag L-cell lines and plays an important role in the secretion of glucagon, GLP-1, and PYY [34]. GPR119 antagonists reduce body weight in obese rats by reducing the consumption of high-fat diet [35] and enhance insulin secretion in diabetic mice. Different types of FA-sensing receptors play a clear role in maintaining metabolic balance in β or endocrine cells.

2.4. Quantitative mechanism of energy substances absorption in the intestine

2.4.1. Quantitative mechanism of carbohydrates

ATP provides the energy required for signal transduction by afferent nerves. It plays an important role in the taste buds along with other signaling molecules [36]. It can help taste buds transmit characteristic signals of taste through autocrine and paracrine pathways [5]. Taste cells also express various proteins such as glucagon, GLP-1, CCK, neuropeptide Y (NPY), peptide PYY [37], vasoactive intestinal peptide (VIP) [38], ghrelin, and galanin, which in turn execute the functions of neurotransmitters and neurohormones. In addition, these peptide receptors are also expressed in taste cells or intraglomerular fibers of afferent taste nerves. Thus, neuropeptides and their receptors play important roles in signal transduction and formation of taste. Researchers speculate that autocrine and paracrine signal transduction mediated by these peptides is likely to be involved in wireless communication between the taste bud cells [39]. Some peptides are likely to play a role in endocrine signaling and control and communication between the brain and peripheral organs. For example, peptides and receptors in the taste buds may respond to peptides and receptors in the circulatory system, thus allowing communication between the intestine and other tissues. This endocrine function can establish a quantitative relationship between metabolism and taste in animals and quantify nutrients in foods [40].

2.4.2. Quantitative mechanism of peptides

GLP-1 is secreted by GI endocrine cells and L cells after food intake [41]. Intake of both fats and carbohydrates stimulates the secretion of GLP-1 in the intestinal tract [42]. The major function of GLP-1 in vivo is to inhibit the pancreas from secreting glucagon and regulating glucose homeostasis by stimulating the secretion of insulin. GLP-1 also inhibits GI motility and secretion and regulates appetite and food intake through the hypothalamus. Increasing evidences support the role of GLP-1 in the peripheral taste control of appetite. This effect is confirmed by flavor sensing of deliciousness, sweetness, and LCFAs [43]. Glucagon is released after proglucagon is broken by protein-converting enzyme PC2. Glucagon induces glycogenolysis in the blood and increases gluconeogenesis in the liver to increase the concentration of blood glucose [44]. Glucagon also stimulates the pancreatic cells to secrete insulin and inhibit the secretion of glucagon [45] to prevent hyperglycemia. Glucagon conducts signal transduction through G protein-coupled glucagon receptor (GlucR). A study has shown that taste cells express glucagon [46]. Similar to GLP-1, glucagon may play a role in taste enhancement and sustainable response control. The most important function of glucagon is to act as a paracrine signal of taste cells. CCK (cholecystokinin) is closely associated with another peptide hormone gastrin. In the GI tract, CCK is produced by type-I cells that are present in the duodenum. CCK promotes digestion by regulating bile and trypsin and activates satiety signals through the hypothalamus. In addition, CCK responds to bitterness and sweetness signals. One of its important functions is to adjust the excitability or depolarization of stimulated taste bud cells.

VIP (vasoactive intestinal peptide) is a peptide hormone, which can be produced in intestine. Although its function was earlier thought to be limited in the GI tract, it is now thought that VIP functions as a neural hormone with central and peripheral nervous activities [47]. The physiological role of VIP is mediated...
via a GPCR: VIP/PACAP (pituitary adenylate cyclase activating polypeptide receptor-1, VPAC1) or VIP/PACAP receptor-2 (VPAC2) [48]. Both VPAC1 and VPAC2 are located in the taste bud cells. Knockdown of genes encoding these receptors in the taste buds affects taste response and expression of GLP-1 and leptin receptors. NPY family and its receptors control energy balance. NPY family of receptors interacts with G-protein-coupled Y receptors (Y1, Y2, Y4, Y5, and Y6) to control energy balance. NPY, CCK, and VIP are expressed simultaneously and may play a role in controlling energy metabolism, appetite inhibition, food intake and regulating gastric emptying. Ghrelin is produced by endocrine cells in the stomach [49] and has multiple functions, including metabolism, reproduction, and immune regulation [50]. It is closely related with the release of appetite-enhancing hormones and growth hormones. In addition, ghrelin transmits signals via G protein-coupled growth hormone secretagogue receptor (GHSR). Ghrelin performs various functions in the nervous system and other peripheral signal transfer systems. Ghrelin is mainly distributed in the central nervous system and GI tract. There are three types of G protein-coupled ghrelin receptors, namely, GALR1, GALR2, and GALR3 [51].

2.5. Quantitative mechanism of fat

Oleoylthanolamide (OEA) is a high-affinity antagonist of endogenous PPAR-α. OEA interacts with its receptors to result in satiety, thus reducing food intake. In addition, OEA signal transmission controls the intake of high-fat diet [52]. OEA dysfunctions lead to overweight and obesity. Fat-sensing receptors identified thus far include membrane protein CD36, namely, G protein-coupled receptors such as GPR120 and GPR40, and TRPM5 [53]. In addition, fat in diet induces satiety signals through biological sensing receptors in the duodenum and jejunum. Emulsified fat significantly inhibits food intake after entering the duodenum [54]. These effects are closely related with the release of two intestinal hormones CCK and 5-HT.

3. Energy storage and oxidation

Energy absorption should obey the law of energy conservation. Although different people have different absorption rates, energy absorbed by the body should meet the following formula:

\[ \Delta E_{\text{in}} = \Delta E_s + \Delta E_c \]

where \( E_{\text{in}} \) is the calorie of total absorbed energy, \( E_s \) is the calorie of stored energy, and \( E_c \) is the calorie of consumed energy.

Fats, carbohydrates, and proteins are called energy substances. Proteins serve as carbon and nitrogen sources. Because energy metabolism is essentially a moderate burning process in which \( \text{CO}_2 \) is generated via decarboxylation under constant temperature and pressure, energy production depends on dehydrogenation and electron transfer to oxygen through oxidation–respiration chain that finally results in the release of water. This process is coupled with ATP synthase complex and promotes phosphorylation of ADP to ATP. Proteins are not optimal energy material because their oxidation results in the formation of nitrogenous compounds whose accumulation can lead to toxicity.

Analysis of formula (1) shows that when energy absorption exceeds its consumption, surplus energy is stored for energy shortage in the future. It is clear that carbohydrates are usually stored in the form of muscle and liver glycogen to supply energy for muscle movement and various physiological activities, especially during stress. However, this storage form cannot change with energy absorption and is not the major mechanism for long-term energy storage. Long-term energy storage only involves conversion of glucose into fat, and this fat is majorly stored subcutaneously, especially under the belly. This storage method is of vital significance for biological adaptation, which not only provides energy to the body in the cold season when food shortage occurs but also effectively prevents heat loss. This storage method provides hibernating animals adequate supply of energy for the recovery in the subsequent year.

However, in advanced animals, such as humans, this storage method has a key problem, in that carbohydrates are converted to acetyl coenzyme A (acetyl-CoA) through the central metabolic pathways, thus resulting in the synthesis of fatty acids that are stored in the form of fat. However, the process is irreversible in human beings and other advanced animals except plants and microorganisms, in which undergo gluconeogenesis to form glucose and other carbon sources via glyoxylate. In other words, the energy stored in human beings in the form of fat can only be decomposed through energy consumption and circulated in the form of ketone bodies. The major component of ketone bodies is \( \beta \)-hydroxybutyrate (\( \beta \)-OHB), which is an energy molecule from fat and is circulated in animals in vivo. This is mainly observed during long-term exercising or fasting. When the body is in a state of starvation, glycogen is the first choice for producing energy, followed by adipose cells or tissues. Fat is mobilized and transported to the liver where they are converted into ketone bodies, which are again transported to the site of energy requirement via the circulatory system and mitochondrial oxidation. Therefore, in addition to a certain function of reservation, accumulation of fat itself is the signal of energy accumulation. In human beings and higher animals, ketone body metabolism is the only way to reduce fat accumulation. Several studies have shown that ketone body metabolism and ketogenic diets play an important role in many diseases caused by metabolic homeostasis and imbalance [55].

4. Energy absorption and metabolic homeostasis

Because of an increase in the number of diseases caused by overnutrition, several studies have focused on the relationship between energy intake and balanced metabolism and health. After the absorption of energy substances such as glucose, the body first activates the secretion of insulin, then inhibits glucagon activity and gluconeogenesis, and finally promotes glycosgenesis. In case of an emergency, the situation is reversed, i.e., the body first activates glucagon and induces insulin resistance to ensure that energy storage and consumption are strictly controlled to balance the metabolism. Diseases occur once the metabolic balance is out of control.
4.1. Control of synthesis and catabolism

Hormone receptors, including PPARs and liver X receptor (LXR), and transcription factors interact and respond to nutrient signals in vivo. Crosstalk between thyroid hormones and fatty acids may involve multiple components such as retinoid X receptor (RXR) heterodimer partners, DNA-binding sites, and cofactors of transcription factors. TR, PPAR-α, PPAR-γ, and LXRs activate nuclear receptor having similar structure and activation mode and undergo heterodimerization with RXR [56]. They have highly conserved DNA-binding domain and zinc finger domain to identify DNA response element. Ligand-binding domain determines specific ligands for each receptor and contains the (a contact) domain to interact with other receptors, coactivators, and corepressors. Recent studies have found that α-glucose and β-glucose phosphate can be directly used as agonists of LXRα and LXRβ, suggesting that LXRs may coordinate the metabolism of glucose and fatty acids [57]. These findings provide additional evidence that glucose and fat metabolism are regulated during metabolic homeostasis by TR/T3 and LXR agonists (glucose and cholesterol) [58] and confirm that coordination of fatty acids and glucose between energy storage and consumption is necessary for maintaining metabolic balance. Limitation of calories in cells or organisms can effectively prolong their lifespan and delay aging.

Cyclic AMP response element-binding protein (CREB), a transcription factor with helix–loop–helix and leucine zipper domains, is expressed and activated during long-term starvation [59]. At the beginning of starvation, pancreatic α-cells release glucagon to maintain glucose level in the plasma. When insulin reaches hepatocytes, glucagon binds to the corresponding GPCRs and switches GDP/GTP to continuously stimulate adjacent membrane-bound adenylate cyclase to convert ATP into cAMP. Intracellular increase in cAMP stimulates protein kinase A (PKA) to catalyze and regulate the dissociation of subunits [60]. However, CREB alone cannot play this role by activating the transcription of its target genes. It combines with CREB-regulated transcription coactivator 2 (CRTC2/TORC2). A previous study has confirmed that CRTC2/TORC2 is the key regulator of glucose homeostasis during starvation [61]. During fasting, CRTC2/TORC2 is present in the nucleus and binds to phosphorylated CREB to enhance the transcription of gluconeogenic genes. Under the action of cAMP and CRTC2/TORC2 for 6 h, liver cells are acylated by histone acetyltransferase p300 to regain the ubiquitination capability. However, when cAMP level is low, another coactivator—NAD-dependent deacetylase-1 (SIRT1)—promotes the deacetylation of CRTC2/TORC2 to promote the degradation of target proteins [62].

During starvation, increased glucocorticoid concentration promotes the expression of gluconeogenic genes through the binding of GR to the promoter region of GRE. GR-mediated transcription also requires various hepatocyte nuclear factors (HNFs) to promote the transcription of gluconeogenic genes for maximum activity. In comparison, during food intake, insulin level is high, transmission of PKA signal is attenuated, PPAR-γ coactivator 1 alpha (PGC-1α) is activated, CREB is dephosphorylated, and transcriptional activity is reduced. Insulin signals to Akt/PKB to drive the phosphorylation of CRTC2/TORC2 and FoxO1 and their transport from the nucleus. Transport of CRTC2/TORC2 from the nucleus attenuates the transcription of PGC-1α, which limits the expression of PGC-1α. High levels of insulin may decrease the abundance and activity of SIRT1, thus promoting a decrease in the transcription of PGC-1α.

These studies enable us to understand various hormones such as insulin, glucagon, glucocorticoids, and leptin that control gluconeogenesis. Insulin and glucagon control FoxO, CREB, CRTC2/TORC2, and PGC-1α and acetylation/deacetylation, thus controlling the expression of gluconeogenic genes during starvation and food intake via synergistic modulation in the presence of C/EBPs and HNFs. Glucose catabolism does not depend on diet or fasting. To ensure maintenance of catabolism and life activities under starvation, the body stimulates gluconeogenesis in cells to supplement blood glucose by controlling glycogenolysis. During food intake, the body activates the synthesis of insulin and promotes glucokinase to synthesize liver and muscle glycogen by using glucose, thus maintaining stable levels of blood glucose.

4.2. Respiration and oxidative phosphorylation

Studies on exercise physiology show that concentration of lactic acid in the blood increases rapidly in the early stage of movement and is maintained at a steady level once it reaches a certain concentration referred to as maximal lactate steady state (MLSS). MLSS is an important index of athletic strength training, fitness, health, and aging status [63–65]. From the perspective of metabolism, after multistep dehydrogenation, glucose transfers electrons to oxygen to produce water through oxidative respiration, thus driving oxidative phosphorylation to produce and release energy (ATP). This is an extremely important process and is the only feasible way to maintain neutral physiological pH and redox balance in the body.

In addition, lactic acid shuttles between cells, organelles, tissues, and organs [66]. The acetyl-CoA produced by the oxidation of fatty acids and carbohydrates is the major approach of respiration and oxidative phosphorylation. When the capacity of oxidative phosphorylation is limited, shuttling of lactate among cells can alleviate the imbalance between oxidative phosphorylation and oxygen supply. Respiration and oxidative phosphorylation are restricted in two aspects: firstly, because of the restriction of mitochondrial oxidative phosphorylation capacity and secondly because of the limitation of synthetic metabolism in which TCA cycle provides carbon sources for various essential amino acids such as oxaloacetate and α-ketoglutарат. The former occurs during high-intensity movement and normal physical activity while the latter occurs during cell proliferation and tumor progression [67]. Circulation of blood lactic acid is an important indicator of oxidative phosphorylation, which has great research and application value in athlete training; adaptation to high altitude hypoxia environment; and evaluation of diagnosis, treatment, and treatment efficacy of diseases such as metabolic syndrome, diabetes, and cancers.
4.3. Lactic acid and metabolic regulation

When mitochondrial oxidative phosphorylation is limited, NADH$^+/H^+$ cannot perform oxidation through the respiratory chain, and pyruvate is needed to generate lactate. Therefore, generation of lactate reflects the state of mitochondrial oxidative phosphorylation in cells, which is an important indicator of limited mitochondrial function. The formation of lactate is regulated by lactate dehydrogenase (LDH), a tetramer containing two subunits (H and M subunits). LDH is expressed differentially in the heart and muscles under genetic control and has five isozymes LDH-1 (H4), LDH-2 (H3M1), LDH-3 (H2M2), LDH-4 (H1M3), and LDH-5 (M4). These isoenzymes differ in their response and sensitivity to regulators and temperatures [68]. Monocarboxylate transporters (MCTs) play an important role in the shuttling of lactate among organelles, cells, tissues, or organs [69]. LDH converts lactate to pyruvate in the liver, reproductive cells, and neurons and results in the production of liver glycogen. In other tissues, lactate is decarboxylated and dehydrogenated to supply energy through oxidative phosphorylation. Lactate is an important regulator of energy homeostasis [70,71]. Several recent studies have reported the metabolism-regulating function of lactate. Lactate is an important energy substance [70] that modulates energy production [72,73] and serves as an energy resource for muscle contraction [74]. In addition, lactate acts as an important signaling molecule [75,76] for cell repair [77], angiogenesis [78], and inflammation signal [79]. It is also an important target for cancer therapy [80,81]. In fact, lactate and its circulation can be used as an important quantitative index of catabolism and oxidative phosphorylation.

4.4. Ketone bodies and metabolic control

Sugar and fat absorbed by the body are used as fuels of energy consumption while the remaining part is stored in the adipose tissue in the form of fat. Glycogen in the muscles and liver is used as the primary raw material during physiological activities and stress. Glycogen is not only used for energy consumption but also as a carbon source for anabolism. However, stored fat can only be used for energy consumption and not for gluconeogenesis and as a carbon source for anabolism. Thus, accumulated fat can only be burned through the formation of ketone bodies. During starvation or long-term physical activity, ketone bodies provide energy by delivering β-OHB to various tissues. Ketone bodies are the only way to mobilize the accumulated fat in animals. Like lactate, ketone bodies are a liquid fuel. Previous studies have shown that β-OHB is a signaling molecule that acts by interacting with cell surface receptors. As an endogenous inhibitor of histone deacetylases, β-OHB plays an important role in energy metabolism and epigenetic inheritance. Furthermore, β-OHB plays an important role in the regulation of metabolism and ketone bodies, control of calorie intake, metabolic diseases and aging [82].

β-OHB has at least two types of ligands that bind to GPCRs of SFCA. One is hydroxyl carboxylic acid receptor-2 (also called Gpr109), and the other is Gi/o-coupled GPCR that is the earliest identified niacin receptor [83]. Later, it was found that this receptor can be activated by β-OHB [84]. Activation of the acceptor by β-OHB reduces lipolysis in adipose cells, which may be a feedback mechanism for controlling a precursor of ketone bodies [85]. β-OHB exerts antagonistic effects on FFAR3 (namely, GPR41) as a Gi/o-coupled GPCR in the sympathetic ganglia and inhibits sympathetic nerves, thus downregulating the metabolic rate in mice [86]. These acceptors, as a part of the GPCR super-family, may play important roles in regulating metabolism, fat intake, nutrient sensing, energy storage, energy consumption, and nerve excitability [87].

In liver, the fatty acid from circulation can be converted as Ketone bodies (mainly β-OHB), which then return to blood circulation. This process is mainly controlled by forkhead box A2, mTOR, PPARα, and fibroblast growth factor 21 [88]. This process is also controlled by desuccinylations or acetylation of sir2u3 (SIRT3). NAD/NADH ratio regulates β-hydroxybutyrate dehydrogenase. All enzymes required for ketone body metabolism contain modification sites for SIRT3. SLC16A6 (solute carrier family 16, member 6), a monocarboxylic acid transporter (MCT), may be involved in the transport of β-OHB out of liver. In addition, various monocarboxylic transporters can help β-OHB transport across the blood–brain barrier. MCT1/MCT2 transports β-OHB to other tissues. Interestingly, MCT also transports lactate between tissues or organs [89].

5. Overnutrition and metabolic syndrome

Overnutrition is a major cause of modern lifestyle diseases. Studies on energy absorption and consumption indicate that appropriate storage of surplus energy is necessary to extend the lifespan of animals and humans. However, the contents of muscle and hepatic glycogen can not go up with the increase of energy substance (calorie). Therefore, surplus energy substances such as fats, carbohydrates, or proteins are usually stored in adipose tissues. Removal of excess fat is essential for better survival. The most important system in advanced animals is the immune defense system. A reasonable assumption is that nutrients absorbed by the body must ensure the operation of the immune defense system, indicating that immune deficiency does not occur unless there is nutrition deficiency (or pathogen invasion such as HIV or congenital genetic diseases). Overnutrition often results in strong immune responses such as allergy and various inflammatory diseases. Other ways to eliminate the over-accumulated energy include improve glucagon secretion, reduce insulin secretion, and induce insulin resistance to inhibit glycogenesis. Excessively accumulated energy can be excreted as urine glucose and by gluconeogenesis. Another method to eliminate the excessively accumulated energy is through cell proliferation. Apparently, unlimited proliferation of various cancer cells can meet this requirement. To avoid the disease, proper physical activity is very essential to burn the accumulated energy.

5.1. Diabetes and insulin

The number of diabetic patients worldwide is too high. According to a 2011 statistics, approximately 90 million patients
have diabetes. Generally, people in richer countries often consume diets containing more carbohydrates and fat and perform less physical activity or exercise, which in turn increases the prevalence of diabetes. In high-income countries, diabetic patients account for nearly 8% of the adult population while in middle-income countries, they account for >10% of the adult population. Higher incidence of diabetes in these countries is mainly because of more people aged below 50 years develop diabetes compared with those in developed countries, indicating a direct correlation between diabetes and a change in lifestyle in these countries [90]. As mentioned above, when absorbed or accumulated energy is too high, mechanisms to increase energy consumption must be initiated by the body. A direct metabolic pathway to consume surplus energy is to increase the consumption of blood and urine glucose. Insulin promotes the synthesis of glycogen and decrease glycogenolysis in the blood or urine. The insulin resistance, as well as the reduction of insulin secretion and activity can increase the carbohydrate consumption. Diabetes can be prevented by inhibiting excessive nutrient accumulation before the body receives a signal to improve energy consumption. Moreover, physical activity and exercise are important to delay or prevent obesity and diabetes [91].

5.2. Cancer and Warburg effect

Although cancers seem to have no obvious correlation with obesity and excessive nutrition, they can eliminate excessive accumulated nutrients. The unlimited proliferation of cancer cells consume large amount of glucose to provide energy for cell proliferation, and obtain the proteins, carbohydrates and other essential substances originated from the carbon source through central metabolic pathways. Warburg effect is the key way for cancer cells firing a plurality of synthetic and metabolic pathways based on various carbon skeletons [67]. Once glucose is converted to pyruvate via glycolysis, the pyruvate is converted to acetyl-coA by the dehydrogenase system. Moreover, like fatty acid oxidation, dehydrogenation and decarboxylation involved in TCA cycle provide energy for cells [92]. However, this is not observed in cancer cells because TCA cycle is the basic pathway in cancer cells to synthesize glutamic acid, aspartic acid, and other important raw materials. Cancer cells can only provide raw materials as carbon source by consuming large amounts of glucose. Moreover, cancer cells derive large amount of energy via lactic acid fermentation [93], which is the well-known Warburg effect. Both cancer and diabetes are dependent on glucose; therefore, diabetes and cancer often share many characteristics, treatment methods, targets, and pathways [94].

5.3. Obesity and inflammation

 Obesity is caused by the accumulation of excessive energy. Fat accumulation occurs when absorption of energy substances such as fats and carbohydrates exceeds their consumption. Energy substances, especially fat, play an important role in the development of obesity [95]. Many studies have shown that obesity is often accompanied by the development of inflammatory diseases. For example, 75–100% obese people develop nonalcoholic fatty liver disease; further, 20% obese people develop chronic nonalcoholic steatohepatitis or even liver cirrhosis, portal hypertension, hepatocellular carcinoma, and other diseases [96–98]. Jorge et al. used inflammasome-deficient mice (Asc−/− mice) and overweight mice to confirm that obesity-induced inflammation is dependent on the activation of Toll-like receptors 4 and 9 (TLR4 and TLR9, respectively). These systematic investigations have proven that complex sensing and interaction between NLRs and TLRs determine the metabolic pattern. Correspondingly, sensing disorder in the intestine can activate inflammasomes. Moreover, excessive fat accumulation in the liver plays an important role in inflammatory response [99]. Thus, from a metabolic point of view, elimination of excessive fat accumulation requires the activation of inflammatory cytokines, which in turn activate the metabolism of fatty acids. The generated ketone bodies in the liver are then released into the circulation and transported to other tissues or organs for further supersession, which usually lead to the inflammation (such as hepatitis). After all, the body cannot go against the law of energy conservation.

6. Nutrition and lifespan

Nutrition, especially sensing and absorption of energy substances, not only plays an important role in the intensity of life activities and storage of energy substances but also controls aging and lifespan. More activity and rapid growth result in shorter life expectancy, and less activity and slower growth result in longer life expectancy. Members of SIRT protein family may play an important role in prolonging lifespan in nematodes. Although results of previous studies are controversial, physiological functions and mechanisms of these proteins have garnered interest [100].

Initially, Sir2 was recognized as an extra gene copy of non-expressible yeast mating type information gene [101]. Later, it was found that the Sir2 protein encoded by this gene has histone deacetylation activity that is dependent on NAD+ [102]. During the process of executing activity, in fact, NAD+ was degraded into nicotinamide and 1-O-acetyl-ADP-ribose [103]. Because NAD+/NADH serve as a cofactor in various metabolic reactions, Sir2 is speculated to perform a sensing role in cell metabolism [104]. This gene has seven homologous genes (SirTI–SirT7) in animals [105]. Proteins encoded by all these homologous genes contain a conserved domain that forms their catalytic core; however, all these proteins show different subcellular localization [106].

Metabolic pathway is considered to be a network. From a traditional view, the activities of enzymes involved in central metabolic pathways can be regulated, but the expression of these enzymes cannot be regulated. However, many recent studies on various enzymes involved in the central metabolic pathway indicate that expression of these genes is regulated by post-translational modification of nucleosome histones. Covalent modification of histones involves phosphorylation, acetylation, and methylation [107]. HATs [108] are special modifying enzymes that catalytically transfer active acetyl group from
acetyl-CoA to amino group of lysine side chain in histones [109]. Molecules involved in nucleosome histone modifications, such as ATP, acetyl-CoA, and NAD⁺/NADH, are closely associated with energy metabolism. Thus, the modification status of histones after translation in the cytoplasm is an indicator of energy-supplying status of the body. Brian et al. [110] applied quantitative mass spectrometry to analyze acetylation kinetics and stoichiometric change in yeast. Their findings indicate an obvious difference in acetylation during growth and dormant periods and dependency on acetyl-CoA concentration. Concentration of acetyl-CoA in the mitochondria is significantly higher than that in the cytoplasm. These results suggest that histone acetylation reflects catabolism of glucose or fat and body’s energy-supplying status through oxidative phosphorylation.

Thus, more energy supply in the body can lead to higher accumulation of energy and exuberant energy metabolism, leading to a shorter lifespan. In contrast, energy restriction, appropriate starvation, or low calorie intake can reduce catabolism and oxidative phosphorylation, thus prolonging the lifespan. Its signaling pathways and logical relationships can be summarized as follows: High-energy nutrients (carbohydrates and fats) are digested and absorbed in the intestine. These nutrients are quantitatively sensed by GPCRs and then absorbed, stored, mobilized, and decomposed for energy supply by hormones secreted by the nerve and intestine–brain endocrine systems. More active catabolism and oxidative phosphorylation for energy supply result in shorter life expectancy and vice versa. Overall regulation of sugar catabolism depends on lactic acid cycle, and the overall regulation of fat catabolism depends on the circulation of ketone bodies. Both the metabolic pathways show crosstalk at acetyl-CoA, ATP, and NAD⁺/NADH. These important compounds in turn regulate catabolism and metabolic homeostasis through post-translational enzymatic modification of histones and enzyme regulation at multiple levels.

7. Nutrition and properties of foods

Functions of any drugs, including functional foods, are reduced with an increase in the duration of application. Repeated and long-term stimuli result in gradual adaptation or tolerance. This is a common phenomenon. However, impact of functional foods on the body is usually evaluated after long-term consumption. According to traditional Chinese medicine, long-term application of the same type of food can result in gradual adaptation or cause bias. For example, resistant starch as an edible fiber cannot be digested and absorbed in the intestine and exerts its physiological functions after bacterial fermentation to SCFAs in the colon [111]. Increasing evidences have shown that resistant starch can reduce the risk of colorectal cancer and colonic neoplasia, thus exhibiting a health-protecting function [112,113]. John et al. [114] conducted a follow-up examination on 463 patients with colon cancer. The results showed that long-term (4 years) consumption of resistant starch could not significantly reduce the incidence and development of colon cancer and Lynch syndrome cancer. Because these experimental subjects have so complicated food structure and dietary habits during the long-term consumption of this dietary fiber, the effect of resistant starch on colon cancer and Lynch syndrome cancer still need to be investigated further.

Although the basic function of food is nutrition, both nutritional and non-nutritional components of food perform important physiological functions [115]. Etiology of metabolic syndromes is extremely complex, and it is not practical to use a single type of medicine or functional food for its treatment. Therefore, it is important to conduct extensive investigations on the properties of functional foods to provide guidance for formulating healthy diets based on the understanding of the immune, endocrine, and metabolic networks. In addition, evaluation of functional foods should be performed to determine their initial effect rather than their long-term effects; this notion is supported by studies on traditional Chinese medicine. In another word, the so called balanced diets imply not only the balance of nutritional components, but also the balance of food properties (warm, cool, cold and mild).

8. Signal transfer of foods

Besides providing nutrition, diet also performs other biological functions. Although its health functions have still not been extensively explored, we believe that diet performs hormone-like and information-transferring functions in individuals with obesity, diabetes, and other metabolic syndromes [116]. Several evidences have confirmed that various nutritional and non-nutritional components of food activate intracellular signaling cascades, thus controlling the health of the body [117].

8.1. Foods transfer signals through signal receptor change

The GPCR family includes many cell surface receptors. They are sensing receptors for light, sound, smell, taste, and different nutrients, which play a key role in the G protein signaling cascades. Genes encoding different GPCRs show different expression patterns in almost all sites related to feeding and survival, especially, at sites that play a major role in sense, smell, taste, nutrient digestion, and absorption. For example, omega-3 fatty acids activate GPR120 receptor to inhibit inflammation and to improve insulin sensitivity [118]. Many amino acids activate various signal pathways. For example, leucine activates mTOR signaling pathway. MTOR is a serine/threonine kinase that regulates cell cycle, cell growth, and insulin activation [119]. Physiological activities of SCFAs are stimulated by intestinal mucosal surface receptors [120]. Receptors of SCFAs, such as FFAR2 (GPR43) and FFAR3 (GPR41), are called orphan GPCRs [121]. These receptors are important targets for treating metabolic syndromes and cancers [122]. Other non-nutritional components in foods, such as phytochemicals (PhC), exert health-protecting effects by interacting with corresponding receptors. Most of these receptors belong to nuclear receptor superfamly and include estrogen receptors such as PPARs, LXRα, farnesoid X receptor, and pregnane nuclear receptor. Signaling pathways of these receptors include phosphoinositide 3-kinase, mitogen-activated protein kinase, and protein kinase C, and involved transcription factors include Nrf2, activator protein-1, and nuclear factor kappa B [123].
Crosstalk among these signaling pathways constitutes a very complex signal control and regulation network. Almost all PhCs inhibit inflammation, thus downregulating innate and acquired immunity, catabolism, and endocrine function. In addition, some oligosaccharides and various viral or bacterial toxins and enterotoxins interact with receptors on the intestinal mucosal surface, such as TLRs, for signal transduction in the body [124].

8.2. Signaling molecule-mediated cell communication network

Results of many studies have shown that various components of diet interact with receptors in the GI mucosa system to regulate hormones, cytokines, and chemokines, thus controlling metabolism and nerve and endocrine networks in the body [125,126]. It is unclear whether consumption of functional food leads to significant changes in the expression of cytokines and other signaling molecules. Cytokines, chemokines, and hormones are being actively investigated in the field of biochemistry, molecular biology, and medicine. Each cytokine performs multiple functions; however, these functions are executed under different conditions. For example, IL-6 performs both proinflammatory and anti-inflammatory functions. It also regulates the metabolism of fatty acids. However, the exact role and biological relevance of these cytokines are unknown.

To resolve these problems, we must clarify a basic biological question. A cell is a basic unit of biological function, and molecules can only execute their biological roles through cells. We have established a wireless communication network model based on these signaling molecules between cells [127]. This network is a directed weighted and naturally occurring network between cells. This established network is different from the neural network that is composed of nerve fibers. The neural network is a wired network that is only formed in the brain, which is its center, and is involved in wired communication with tissues and organs. Although the wired neural network shows fast electrical signal transmission (nerve excitation), it cannot establish a direct communication between mobile cells such as red blood cells and white blood cells in the blood, tissues, and organs. Wireless communication network uses signaling molecules, including cytokines, chemokines, and hormones, that are transmitted through the circulatory system and cell surface receptors that receive these signaling molecules and initiate an intracellular signaling cascade for signal amplification. The wireless communication network establishes communication not only between organs or tissues and stationary cells but also between mobile and stationary cells [128–130]. This wireless communication network is not a new concept. Cytokine network is usually mentioned as a cellular wireless communication network. However, this network includes other components in addition to cytokines because cytokines do not directly interact with each other.

The earliest model of cell communication network by using cytokines as the signaling molecules was established by Frankenstein et al. [131]. He analyzed cytokine databases to establish a complex cellular communication network. Through comparing 100 different networks that have been investigated, he found that the communication network density in immune cells is the highest (up to 0.6), which is much higher than the neural network density (0.15) in monkey brain. Density of the communication network involving communication between immune and non-immune cells via cytokines was the second highest, with a density of 0.40.

8.3. Quantification of the wireless communication network between cells

Current research in life science is mainly focused on the construction of undirected unweighted networks such as metabolic network [132,133], protein–protein interaction network [134,135], and protein–immunoglobulin network [136] and directed unweighted networks such as neural network for simulating and analyzing the development and evolution of the complex system. However, in various biological fields, directed weighted networks such as metabolic network, group-feeding network, and group network formed by microecological system are the general networks.

To quantitatively analyze the wireless communication network between cells as a complicated nonlinear system, we put forward a mathematic model with multiple parameters, especially the clustering coefficient considers both the direction and the strength of the interaction between nodes, and is a more scientific and quantitative characterization of this kind of network index. Undirected unweighted network is a simplified form of weighted network (unpublished data). In short, the network, especially the directed weighted network, provides various quantitative parameters for the complex nonlinear system from different angles and provides novel avenues or strategies for quantitative analysis and dynamic evaluation of the GI microecosystem and metabolism of biological functions of foods and drugs both in vitro and in vivo.

9. Metabolism and metabolic flux analysis

Although studies on metabolic pathways and networks have made great progress, these metabolic pathways and networks are obtained through speculation based on in vitro data and structures of enzymes and substrates as well as products so that they are not the actual situation of the cells or organism metabolism. In fact, according to free energy change, reversible or irreversible steps based on the speculation of rate-limiting step and enzyme can result in fatal challenge in the application of metabolic engineering [137,138]. Many studies have shown that these rate-limiting steps or enzymes may not exist [139].

In other words, metabolic networks and pathways are the summary and speculation, and the actual situation still needs to be explored systematically and quantitatively. The actual metabolism after food consumption in vivo is still poorly understood. Different situations of the body can present different metabolic statuses. If energy is required, catabolism will increase. After a meal, anabolism will improve. Metabolism status is not same in different organs, tissues, and cells. Therefore, it is critical to understand how communication and coordination
of nutrients and energy metabolism in organs, tissues, and cells are conducted by performing quantitative analysis.

9.1. Clarification of metabolic homeostasis by chemometrics

Food intake not only provides nourishment to the body but also transfers energy and molecules to the body through the GI sensing system. Physiological activities of foods in the body are regulated through nerve (wired communication) and immune and endocrine (wireless communication) networks. From the perspective of molecular biology, gene expression and regulation by different foods is complex because large number of genes is involved. However, from the perspective of metabolism, it is simple because it mainly involves energy and material metabolism, including anabolism and catabolism. Anabolism and catabolism are also connected to the central metabolic pathways. Importantly, quantitative description of metabolic networks should be conducted through chemometrics. Unfortunately, the roles of foods in *in vivo* metabolic network are less understood thus far.

9.2. Properties of foods determined using central metabolic flux analysis

Metabolic network and metabolic control analysis have been mainly studied in model organisms such as *Escherichia coli* and yeast, because quantitative expression and synthesis of different enzymes involved in metabolic pathways can only be achieved through genetic operation, thus accomplishing the control for metabolic flux (also called flux control coefficient) by changing the expression of various enzymes. However, it is impossible to achieve different expression of enzymes in metabolic pathways through flux control analysis because mutations in enzymes involved in the central metabolic pathways are often fatal. In addition, error tolerance capacity of regulatory enzymes can often result in no change in phenotypes. Flux control analysis needs to be conducted in a steady state, which further limits its popularity and application. Our investigations have found that expression of different enzymes involved in metabolic networks can be changed by changing environmental temperature and activity status of organisms. Metabolic fluxes (variables) are subjected to differential treatments to perform flux control analysis of metabolic networks. By using these methods, we have conducted flux control analysis of metabolic pathways in rice, *Lactobacillus helveticus*, spirulina, toad, ground squirrels, human, and melon [140], which proves the feasibility of flux and flux control analysis for the functional evaluation of foods *in vivo*. Based on these investigations, we analyzed flux change in lactate metabolism due to different foods consumed by volunteers and found that lactate metabolic flux can be used as the important index of energy supply from catabolism and oxidative phosphorylation. Foods with hot properties increase the metabolic flux of lactate, whereas those with cold properties decrease the metabolic flux of lactate (unpublished data). Therefore, flux and flux control analysis of metabolic network can quantitatively describe the effect of foods on the control of catabolism and anabolism in the body. At present, many diseases are correlated with overnutrition and lifestyle. Therefore, metabolic flux analysis has important application value. Interestingly, metabolic and corresponding flux networks are similar to wireless communication network. Both these networks are directed weighted networks [141].

10. Key problems that need to be resolved to understand the relationship between foods and health

In term of the relationship between foods and health, the following four key problems have to be addressed: (1) Undernutrition causes nutrition deficiency, and overnutrition leads to obesity, hypertension, hyperlipidemia, diabetes, and cancer. It also highlights that nutritional requirements of the body may vary among different individuals with different heredity and family backgrounds, different dietary habits, and living in different countries. Even different gut microbes may affect the requirement of nutrition. Although a research on personalized nutrition and nutritional genomics is proposed, results from epigenetic studies have shown that dietary habits and experience of a person can change epigenetic characteristics through DNA imprinting and histone modification. This indicates that dietary requirements are not decided by genome. Diets determine the expression, regulation, modification, imprinting, and heredity of the genome without altering DNA sequences. Obviously, this is a challenge for nutritional genomics. Thus, the problem seems to be at the origin, i.e., how to provide a scientific diet and formula for different individuals? (2) Contribution of foods and nutrition to the immune system is apparent, which is also a hot topic of research on functional foods. However, increasing number of studies indicate that immune defense is the first priority of nutrition. Hypoimmunity is only observed in infants, children, and elderly and in individuals with diseases and serious nutrition defects. Thus, when nutrition is abundant, even commonly redundant, excessive immunity can cause inflammation, autoimmune diseases, and metabolic syndromes. Like a double-edged sword, immunity can cause diseases when it is too low or too high. Therefore, the question is what is the appropriate immunity and how should it be quantified. Unfortunately, no method is available to quantify the immune system thus far. (3) Another prominent problem is that experimental and efficacy evaluation methods are usually obtained from the pharmaceutical field, namely, *in vitro* experiments and experiments in animal models. However, the dietary structures, habits, and behaviors between human beings and animals are different. Therefore, it is difficult to find experimental animals that are similar to humans in terms of food processing. The major reason for using experimental animals for testing functional foods is that some researchers believe that the protective (healing) effects of foods on the body can only be evaluated using corresponding tissues or organs, which makes experimental animals necessary. (4) Precise effect of foods on organs or tissues within the body is unclear. Previous studies have shown that food mainly interacts with the GI mucous membrane system. Communication between organs and tissues is established through the circulatory and signaling systems of the GI tract and inner system. Food does not enter
target organs or tissues directly, which results in the major problem that we face, i.e., the quantitative description of this complex nonlinear system. The metabolic and cellular communication networks provide feasible ways and can be evaluated by obtaining only a few millimeter cube of peripheral blood.

11. Summary and prospect

Traditional nutrition is a science to provide basic nutrients to the body. However, when nutrition, especially the absorption of energy substances, exceeds the demands of the body or even accumulates excessively in the body, more energy consumption is required to dispose of the superfluous storage. The body has a perfect nutrition sensing and counting system to maintain a balance among caloric absorption, storage, and utilization. This forms the nutritional sensing system with GPCRs as the major components that absorb and control nutrition through calcium channels, sodium–potassium pumps, and autonomic nervous system. Nutrient-sensing system with mTOR as the major component can control nutrition storage, distribution, and utilization in vivo. Disordered control can lead to metabolic diseases and even cancer.

Excessive nutrition is closely correlated with appetite disorders. Appetite control depends on dietary structure and lifestyle, autonomic nervous and GI mucosa sensing systems, and interactions between various ingredients in foods and corresponding receptors. Therefore, understanding the interactions between food components and GI mucosa sensing system, especially sensing, signaling pathways, and interaction between the nutrient-sensing system with GPCRs, is essential for improving public health.

Storage and utilization of energy substances involve two different controlling processes. In advanced animals, glucose is stored in the form of hepatic and muscle glycogen, and glycogen is re-used by phosphorylase. Fatty acids are stored in the form of fat, especially hypodermic fat, and provide energy to the body through β-oxidation. When energy substances exceed storage capacity, the body initiates an “alarm signal”, eliminates accumulated energy directly by improving catabolism or in the form of blood or urine glucose, promotes cell proliferation, produces excessive immunity, and even causes cancer. These processes are controlled by mTOR nutrient-sensing system.

Discovery of longevity genes such as SirT gene family has resulted in tremendous enthusiasm among many scientists. Numerous studies have shown that this gene family uses intermediate metabolites such as acetyl-CoA, ATP, and NAD + or nucleosides to modify and control the activity and expression of enzymes involved in the central metabolic pathways. SirT gene can prolong lifespan by reducing catabolism. In contrast, the body can strengthen catabolism and cell proliferation during overnutrition so that it is inevitable to cause various diseases and even shorten lifespan.

As emphasized by Ryan and Seeley [117], foods and nutrition are the basis for biological subsistence. Moreover, due to hormone-like activity, they transfer various signals to the body to control the metabolism and physiological activities through complicated interactions with the GI system and cell receptors in vivo. Meanwhile, many compounds from fruits and vegetables, although not considered as nutrients, regulate life activities such as appetite and basic metabolic status by interacting with receptors. Studies on these issues may provide us personalized nutrition and food recipes. Future research should focus on GPCRs, mTOR, TLRs, and nuclear receptors and their interactions with diet compositions. Studies on signal functions of all nutrients should also be performed.

Because of different diets and genetic backgrounds, it is impossible to provide an identical diet recipe to different people. Studies indicate that long-term consumption of the same type of functional food can not only eliminate its function but also cause diseases because long-term dietary bias. Therefore, we should not focus on the so-called “efficacy” from long-term consumption of functional foods but should explore the properties of various foods to provide dietary plans to different people based on their physical conditions and the properties of the food. These dietary plans will have a balance of both nutrition and food properties.

After years of efforts, we have established a set of methods suitable for the functional evaluation of foods and drugs in vivo, i.e., intercellular wireless communication network. Because it is a directed weighted network, it enables us to quantitatively depict its characteristics by using various parameters from various angles referring to biological macromolecular interaction network models, i.e., the undirected unweighted network and directed weighted metabolic network. Foods are closely correlated with nutritional metabolism. We have successfully created flux and flux control analysis suitable for the study based on the central metabolic pathway in human body. This established method can quantitatively evaluate the effects of foods on metabolic network because it quantitatively explores the roles of foods in synthesis and catabolism in vivo. In addition, because the analysis involves obtaining peripheral blood, it serves as a noninvasive method to provide a novel strategy for the quantitative evaluation of functional foods in vivo.

References


