Research
Animal Nutrition—Perspective

Nutrient Sensing for the Future of Land Animal and Aquaculture Nutrition

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ABSTRACT

Feeding is vital for animal growth and the maintenance of health. However, the underlying mechanisms that mediate dietary performance have long been a so-called black box. It is only during recent years that studies have demonstrated that nutrients act as signals that can be sensed by cells and organisms and that play vital roles in gene expression and metabolism. Multiple signaling pathways have been identified as being responsible for the sensing of discrete nutrients. While successes have been achieved in the exploitation of nutrient-sensing signals in drug discovery and disease control, applications based on the sensing and metabolic control of major nutrients (proteins, lipids, carbohydrates, etc.) in aquaculture and land-farmed animals remain in their infancy. We thus provide a tentative perspective on future research topics and applications of nutrient sensing in animal nutrition.

1. Introduction

Nutrition is vital for the growth and health of animals. Nutrients—especially macronutrients, including amino acids, fatty acids, and carbohydrates—provide energy and basic building blocks that are needed for homeostasis and biomass accretion. Traditionally, nutrition science has focused on the physiological processes of digestion, absorption, transport, and metabolism [1]. However, starting in the beginning of this century, a great deal of attention has focused on how cells and organisms sense and metabolically respond to nutritional status through what is known as nutrient sensing—a topic that has become a hot spot in the biological sciences [2]. Numerous studies have demonstrated that nutrient sensing plays critical roles in the regulation of food intake, energy expenditure, hormone secretion, and metabolic processes in humans and other animals [2–6].

2. Cellular nutrient-sensing pathways

2.1. Amino acids sensing

Mechanistic target of rapamycin (mTOR) signaling has become known as the major signaling hub for sensing the availability of

nutrients, especially amino acids, and regulating the balance of anabolism versus catabolism in cells [7,8] (Fig. 1). mTOR complex 1 (mTORC1) comprises serine/threonine kinase mTOR, raptor (a regulatory protein associated with mTOR), Dishevelled, Egl-10 and Pleckstrin (DEP) domain-containing mTOR-interacting protein (DEPTOR), and mLST8 (mammalian lethal with Sec13 protein 8) [9]. Among the many downstream effectors of mTORC1, 4E-binding protein 1 (4EBP1) and the p70 ribosomal S6 kinases (S6K) are the fundamental players in messenger RNA (mRNA) translation, protein synthesis, and cell proliferation regulation [8,10]. Small guanosine triphosphatase (GTPases), such as Rag and Rheb (Ras homolog enriched in brain), are crucial for transducing nutritional input and mTORC1 activation [11–13]. mTORC1 receives signals from growth factors that involve signaling cascades consisting of cell surface receptors, Akt, tuberous sclerosis complex (TSC), and Rheb interactions with mTORC1 [8]. The activation of mTORC1 by Rheb also requires the lysosome localization of mTORC1 and is mediated by the Rag GTPases heterodimers of RagA/B bound to RagC/D [12,14]. The GTP-loaded Rag GTPases recruit mTORC1 to the surface of lysosomes when nutrients—especially amino acids—are available [13].

In recent years, a growing number of proteins have been identified as amino acid sensors that bind distinctive types of amino acids and act as modulators of mTORC1 activities through modulation of the Rag GTPases or mTORC1 complex localization [15–23]. SLC38A9, a lysosomal transmembrane protein with homology to
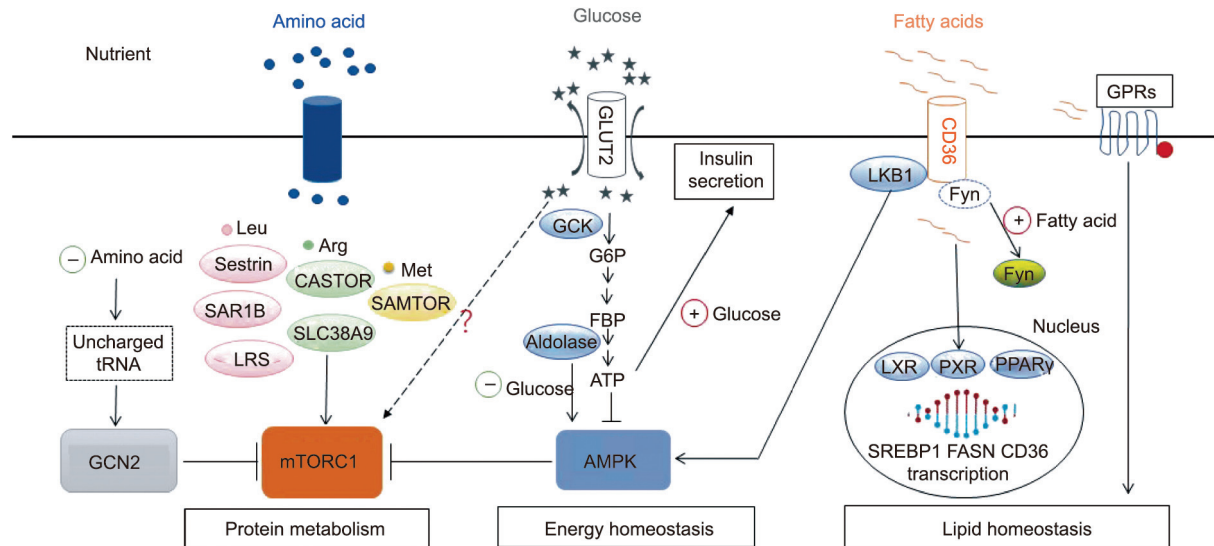
Fig. 1. Major nutrient sensing signaling pathways. tRNA: transfer RNA; GCN2: general control nonderepressible 2; Leu: leucine; Arg: arginine; Met: methionine; SAR1B: secretion associated ras related gtpase 1b; LRS: leucyl-tRNA synthetase 1; CASTOR: cytosolic arginine sensor for mTORC1; SLC38A9: solute carrier family 38 member 9; SAMTOR: S-adenosylmethionine sensor upstream of mTORC1; GLUT2: glucose transporter type 2; GCK: glucokinase; G6P: glucose 6-phosphate; FBP: fructose-1,6-bisphosphate; ATP: adenosine triphosphate; AMPK: adenosine monophosphate-activated protein kinase; CD36: cluster of differentiation 36; LKB1: liver kinase B1; Fyn: Src family tyrosine kinase; LXR: liver X receptor; PXR: pregnane X receptor; PPARγ: peroxisome proliferators–activated receptor γ; SREBP1: sterol regulatory element binding transcription factor 1; FASN: fatty acid synthase; GPRs: G protein-coupled receptors.

amino acid transporters, can sense the arginine (Arg) levels within lysosomes and activate the Rag GTPases through non-canonical guanine nucleotide exchange factor (GEF) mechanisms [15,24–26]. Cytosolic Arg sensor for mTORC1 (CASTOR)1/2 (a cellular arginine sensor for mTORC1) has been identified as a cytosolic Arg sensor that negatively regulates the mTORC1 pathway by binding and inhibiting GATOR2, a positive regulator of the nutrient-sensing pathway [16,17]. Secretion associated ras related gtpase 1b (SAR1B) has been found to function with sestrins to sense levels of leucine (Leu) and regulate mTORC1 signaling [21]. Intracellular methionine levels can be sensed by S-adenosylmethionine sensor upstream of mTORC1 (SAMTOR), which regulates mTORC1 signaling through GATOR1 [23].

General control nonderepressible 2 (GCN2) kinase functions as a sensor for amino acid deficiency [27]. An amino acid shortage leads to the accumulation of uncharged aminoacyl-transfer RNA (tRNA), which binds to the aminoacyl-tRNA synthetase-like domain of GCN2, and then to phosphorylate eukaryotic translation initiator factor 2α (eIF2α) in turn, and thereby suppresses general protein synthesis [28]. While these amino-acid-sensing pathways are ubiquitously expressed, their activities are regulated in a tissue-specific manner [29].

2.2. Lipid sensing

The fatty acid transporter cluster of differentiation 36 (CD36) is considered to play an important role in lipid sensing [2] (Fig. 1). Under the condition of fatty acid deficiency, CD36 forms a complex with Src kinase Fyn and AMPK kinase LKB1. When fatty acids are abundant, their interaction with CD36 dissociates Fyn from the protein complex, allowing LKB1 to activate AMPK [30]. Multiple G protein-coupled receptors (GPRs) respond to different types of fatty acids (Fig. 1). For example, GPR40 and GPR120 respond to medium- and long-chain fatty acids, GPR41 and GPR43 to short-chain fatty acids, and GPR119 to lipid derivatives [31–33]. Lipid-sensing nuclear receptors, including liver X receptor (LXR), pregnane X receptor (PXR), and peroxisome proliferators-activated receptor γ (PPARγ), can interact with fatty acids and cholesterol to

modulate the transcription of lipid metabolism-related genes such as *FASN*, *SREBP1*, and *CD36* [34,35]. The sterol regulatory element binding transcription factor 1 (SREBP1) cleavage activating protein (SCAP) is a cholesterol-sensing protein that binds to cholesterol and regulates SREBP1 transcriptional activity [36]. Carnitine palmitoyltransferase-1 (CPT-1) regulates the entry of long-chain fatty acyl-coenzyme A (LCFA-CoA) into mitochondria for β oxidation. It also affects multiple processes, from insulin resistance and insulin secretion to appetite control, and plays diversified roles in the brain, liver, pancreas, and muscle [37].

2.3. Glucose sensing

Glucose is sensed in different tissues, including the pancreatic islets, liver, muscle, hypothalamus, and adipose tissue, and is interlinked with hormones and metabolic fluxes. The glucose metabolism and signals are regulated by tissue-specific factors and the nutritional status of the tissue [38]. The first step in glucose utilization is the phosphorylation of glucose by glucokinase (GCK), which also functions as a glucose sensor [2] (Fig. 1). GCK has a significantly lower affinity compared with other hexokinases and is only active under the condition of glucose abundance [39]. GCK is highly expressed in liver, the most active metabolic organ [40]. The specific expression pattern allows the GCK-generated glucose 6-phosphate (G6P) to be shunted into glycolysis or glycogen synthesis according to the metabolic needs (i.e., for energy production or storage) [2]. While the GCK functions as an intracellular glucose sensor, the membrane-located glucose transporter type 2 (GLUT2) can sense extracellular glucose levels. Similar to GCK, GLUT2 has a relatively low affinity to glucose, allowing it to only import glucose under high glycaemia conditions. Furthermore, GLUT2 can transport glucose bidirectionally [41,42]. Thus, GLUT2-mediated input occurs during transient hyperglycemic states, and GLUT2-mediated output occurs when the intrahepatic glucose levels are high, making GLUT2 a key controller of glucose homeostasis [2]. GLUT2 is expressed in multiple tissues. In pancreatic β-cells, GLUT2 is required for glucose-stimulated insulin secretion. In the nervous system, GLUT2-dependent glucose sensing controls feeding and thermoregulation [41].

Insulin and glucagon are two hormones that control glycaemia. Increased glucose uptake elevates the intracellular adenosine triphosphate (ATP) levels in β-cells; this is followed by the closing of membrane potassium channels and membrane depolarization, which in turn cause a transient intracellular calcium pulse and insulin secretion [43]. Sodium–glucose luminal transporter-1 (SGLT-1) mediates the transport of glucose into the enteroendocrine cells and initiates subsequent signaling through the secretion of gut hormones such as glucagon-like peptide (GLP)-1 [44]. Glucose sensing is also achieved by the taste receptor T1R2-T1R3 heterodimer on enteroendocrine cells, which plays a role in triggering the secretion of incretin hormones for improved glycemic and lipemic control [45]. Glucose levels can also be indirectly sensed by two key metabolic regulators: AMPK and mTORC1 signaling. For example, aldolase senses a low level of glucose metabolic intermediate fructose-1,6-bisphosphate (FBP) and active AMPK signaling [46]. The mechanisms of glucose-regulated Rag GTPases and mTORC1 activation is still unclear [47].

3. Regulation of nutrient sensing in mammalian growth and disease

Nutrient-sensing signaling pathways—and mTOR in particular—receive external nutrients and environmental inputs to regulate biomass accretion and health. Dysregulated sensing signals have been shown to be involved in pathological processes such as cancer, cardiovascular diseases, and neurodegenerations [48–50]. Lack of mTOR activity leads to early-onset myopathy and hinders growth in mice [51]. mTOR is also an important regulator of immune responses. Accumulated evidence shows that mTOR promotes the differentiation, activation, and function of T cells, B cells, and antigen-presenting cells [52,53]. Furthermore, mTOR activities are involved in driving the growth and proliferation of stem and progenitor cells, and in dictating the differentiation program of multipotent stem cell populations [54,55]. In particular, mTOR regulates multiple intestinal epithelial cell lineages and promotes stem and progenitor cell activity during intestinal epithelium repair post injury [56–58]. Taken together, this evidence highlights the importance and necessity of understanding and manipulating nutrient sensing in animals.

4. Nutrient-sensing studies in animal nutrition

4.1. Nutrient sensing in land-farmed animals

Numerous studies have confirmed the fundamental roles of nutrient sensing in farmed animals, both *in vitro* and *in vivo*. Most nutrient-sensing molecules and functions for amino acids, lipids, and carbohydrates are well conserved in farmed animals such as pigs [59]. Methionine, Leu, Arg, and other amino acids have been found to activate the mTOR pathway in cell lines from quail, cow, porcine, and other domesticated animals [60–62]. In addition, branched-chain amino acids are able to activate the mTORC1 pathway in lactating cows and piglets *in vivo* [63]. Long-chain fatty acids stimulate the release of GLP-1 and GLP-2 from porcine ileal tissues [64], while linoleic acid input has been specifically correlated with CD36 levels in the skeletal muscle of broilers [65]. The phosphoinositide 3-kinases (PI3K)–protein kinase B (PKB)–mTOR pathway has also been found to be involved in the infections of porcine epithelial diarrhea virus [66]. Dietary Leu supplementation could attenuate the decrease of mucin production in the jejunal mucosa of weaned pigs infected by porcine rotavirus [67]. General decreases in villus height and intestinal dysfunction during weaning have been found to be accompanied by reduced mTOR activities in piglets [68]. Dietary supplementation of glutamate improved mTOR signaling, suppressed inflammation, and alleviated intestine injury in weanling pigs challenged with lipopolysaccharide [69]. mTOR activators, including branched-chain amino acids, have also been found to enhance muscle growth in weanling piglets [70,71].

Nutrient sensing in the intestine plays a fundamental role in signaling the nutritional status to the central nervous system and regulating feeding behavior in pigs [59]. Artificial sweeteners, which are routinely included in piglets' diet to reduce post-weaning enteric disorders and promote growth, are now believed to function through enhanced sodium–glucose luminal transporter-1 (SGLT-1) activity and glucose absorption [72]. Taste receptors and nutrient sensors in the intestine also play key roles in food intake and appetite control in chickens [73].

4.2. Nutrient sensing in aquaculture

Nutrient sensing has received a considerable amount of attention in aquaculture species in recent years and has been comprehensively reviewed elsewhere [3,6]. Fish share the main regulatory networks of growth, feeding, and metabolism with other vertebrates. Nutrient-sensing signaling pathways, including mTOR, peroxisome proliferators–activated receptors (PPARs), and AMPK, are also highly conserved in fish [4,74,75]. Nevertheless, there are also unique features of nutrient sensing in fish. For example, as poikilotherm animals, fish respond to cold resistance by stimulating lipid catabolism and autophagy, and require nutrient-sensing signaling such as the Carnitine palmitoyltransferase-1 (CPT-1) and mTOR pathways [76]. Also, peroxisome proliferators-activated receptors α (PPARα), the critical modulator for lipid catabolism in both mammals and fish, has been found to not be activated by a high-fat diet in Nile tilapia (*Oreochromis niloticus*), although it can be activated by a high-fat diet in mammals and stimulates lipid breakdown. This finding suggests that the self-protective mechanism of fish in response to high energy intake has not been well established from an evolutionary perspective [77]. Nutrient sensing after meals is present in multiple tissues in fish, such as the intestine, liver, pancreas, muscle, and brain (hypothalamus) [3]. Nutrient-sensing systems may detect nutrients either directly or indirectly by sensing some derived metabolite that reflects nutrient abundance.

Digestive enzymes, endocrine peptides, and hormones are responsive to food ingestion. The hypothalamus has been demonstrated to be a signaling integratory center for nutrient sensing and regulating appetite through anorexigenic and orexigenic neuropeptides [6]. Nutrient sensing in the central nervous system coordinates with that in the periphery to modulate metabolism in organs through secreted neuropeptides and hormones [78]. Early studies have demonstrated that mTOR activities are responsive to feeding and regulate metabolic processes, including protein synthesis, glycolysis, gluconeogenesis, lipogenesis, and so forth [79,80]. The fatty acids sensor CD36 is expressed and regulated by diet in the silver pomfret (*Pampus argenteus*), grass carp (*Ctenopharyngodon idella*), Atlantic salmon (*Salmo salar* L.), and large yellow croaker (*Larimichthys crocea*) [81–84]. Dysregulated PPAR signaling was found to be closely related to fatty liver disease in Nile tilapia [85]. Similarly, dietary carbohydrate levels influence levels of glucose-sensing molecules such as glucokinase (GK) and GLUT2, as well as AMPK signaling [78,86–88].

Compared with terrestrial animals, fish require a high level of dietary protein, optimally from fishmeal, which is a limited natural resource that is unsustainable for the development of aquaculture [89]. Replacing fishmeal with plant proteins in aquafeeds has been a long-term goal, and a great deal of effort has been made in this endeavor. Regardless of the trend of reduced fishmeal inclusion in fish diets, however, it is generally acknowledged that the performance of fishmeal is superior to that of other protein sources [90].

Our previous studies demonstrated that, after fishmeal replacement with other protein sources, the postprandial activation of mTOR signaling was reduced and thus provided less drive for anabolic processes after feeding in turbot (*Scophthalmus maximus* L.) [91,92]. We further showed that imbalanced amino acids [93] and anti-nutritional factors such as gossypol [94], saponin [95], and lectin from plant proteins [96] all contribute to the inhibition of mTOR activation in fish. Supplementation of mTOR activators, such as branched-chain amino acids [97], glutamate [98], and phosphatidic acid [99], could be beneficial for dietary utilization and growth in various fish species. We also found that targeting the nutrient-sensing pathway by simply increasing feeding frequency could fine-tune postprandial responses and improve fish growth by 7.68% and protein retention by 4.01% in turbot [97].

5. Integration of nutrient sensing with animal nutrition: What can we do next?

Numerous studies have unequivocally demonstrated that nutrient sensing plays major roles in the regulation of metabolism and diseases. There have been extensive applications of nutrient sensing in clinics. For example, various forms of fasting, protein restriction, and specific reductions in the levels of essential amino acids such as Met and the branched-chain amino acids are practiced in order to selectively impact mTOR and AMPK signaling to promote healthy longevity [100]. The modulation of nutrient-sensing pathway therapeutics—particularly growth hormone secretagogues—has been developed to improve cognitive outcomes [101]. In contrast, the merging of nutrient sensing with animal nutrition is still in its infancy. From our point of view, research in the following directions, at least, is much needed and will be beneficial to the future of animal nutrition:

● **Correlation of nutrient-sensing responses with feed formulations.** To date, most of the studies on this topic have been conducted to elucidate the fundamental mechanisms of nutrient sensing toward defined nutrients, either using cell lines *in vitro* or animal models *in vivo*. However, practical diet formulations are much more complex. Traditionally, dietary performance is evaluated by phenotypic parameters such as growth rate, feed conversion efficiency, protein retention rate, and so forth. Elucidation of the correlated nutrient-sensing responses should be valuable for an understanding of the mechanisms underlying dietary performance, and for instructions for further feed optimization.

● **Integration of nutrient sensing with new methodologies for future nutrition science.** Isotopic labeling with a flooding dose has been used for the measurement of protein synthesis rate for decades [102]. However, metabolic flux analysis (MFA) has only recently emerged as an important tool for studying metabolism quantitatively [103]. The conceptual idea of MFA is that the isotope-labeling patterns of intracellular metabolites are determined by fluxes; therefore, by measuring the labeling patterns, we can infer the metabolic dynamics quantitatively. The wealth of omics technologies, such as genomics, transcriptomics, proteomics, and metabolomics, has been well exploited by nutrition science to explore the interactions of foods with biological systems. A tremendous amount of data has been collected and analyzed using system biology methods to process genomic, mRNA, protein, and metabolite information for the comprehensive description of molecular network regulation. Nevertheless, high-throughput profiling information needs to be categorized and interrogated. It is only once the activities of the signaling pathways that sense nutrients and intermediate metabolic processes are delineated that we can obtain a functional map of how cells and organisms act in concert.

● **Precision nutrition with targeted nutrient-sensing intervention**. Nutrient-sensing molecules—and mTOR in particular—have been exploited as therapeutic targets in drug discovery. Precise nutritional strategies have also been proposed to modulate nutrient-sensing responses and promote healthcare against cancer [104], Alzheimer's disease [105], Down's syndrome [106], and sarcopenia [107], among others. Nutrient sensing also opens up a new avenue for animal nutrition. Guided by postprandial nutrient-sensing kinetics, systematic feed optimization can be done in order to achieve economically valuable output. The time has come to integrate the theory of nutrient sensing and high-throughput technologies with traditional nutrition methods, and to carry out large-scale pilot trials for precision nutrition, which should pave the way for the future of animal nutrition.

● **Development of biomarkers and devices for real-time animal monitoring.** There are features of nutrient-sensing molecules such as mTOR that render them potentially useful as biomarkers: Their activities are responsive to nutritional status in a dose-dependent manner [92,97,108], and they are vital for organ-specific functions, including muscle protein deposition and immune responses, which can be measured and employed as surrogate outcomes. A great deal of effort is needed to screen and select potential candidates as useful biomarkers for the indication of the nutritional and health status of farmed animals. We have seen rapid development of the integration of biosensing technologies with the Internet of Things (IoT) paradigm to promote rapid, on-farm, and real-time monitoring of the health and welfare of farmed animals, especially cattle [109]. Conceptual sensors have also been developed to monitor nutritional status in animals [110]. Nevertheless, it is still necessary to tailor technologies efficiently and accurately for particular physiological purposes and species-specific traits. Such data should be valuable for future precision animal farming.

Compliance with ethics guidelines

Zongyu Gao, Chengdong Liu, Kangsen Mai, and Gen He declare that they have no conflict of interest or financial conflicts to disclose.

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