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# 陆生和水产养殖动物营养感知理论和应用展望

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**摘要**

饲料在动物生长和健康中扮演着重要的角色，然而长期以来，营养调控的内在机制一直是动物营养学研究的“黑匣子”。直到近年来，多个感知不同营养素的信号通路被揭示，研究发现营养素能够作为信号分子被细胞感知，并在调控机体基因表达和代谢活动中起着至关重要的作用。目前营养感知机制已经被应用在药物开发和疾病控制中，但在水产和陆生养殖动物中，基于主要营养素（蛋白质、脂质和碳水化合物等）的营养感知和代谢调控的应用研究仍处于起步阶段。在本文中，我们综述了营养感知理论的前沿进展，并对未来营养感知理论在动物营养中的应用提出一些设想和建议。



## 1. 引言

营养对于动物的生长和健康至关重要，其中大分子营养素如氨基酸、脂肪酸和碳水化合物等，既能为生物体提供能量和维持生物体稳态，也是生物体组织细胞的基本组分。传统上，营养科学主要关注消化、吸收、运输和代谢等生理过程[1]。然而，直到21世纪初，细胞和生物体如何感知和代谢性地响应营养状况，即营养感知，才引起了广泛关注，成为整个生物科学的热点[2]。大量研究表明，营养感知在人类和不同动物的摄食、能量稳态、激素分泌以及代谢的调控中发挥着关键作用[2–6]。

## 2. 细胞营养感知的信号通路

### 2.1. 氨基酸感知

雷帕霉素靶蛋白复合物1（mechanistic target of rapamycin complex 1, mTORC1）是细胞感知营养物质（尤其是氨基酸）的主要信号中枢，其能够感知细胞营养状态，进而调节细胞合成代谢与分解代谢的平衡[7–8]（图1）。mTORC1是由mTOR、raptor (regulatory-associated protein of mTOR)、DEPTOR (DEP domain containing MTOR interacting protein)和mLST8 (mammalian lethal with Sec13 protein 8)结合形成的复合物[9]。在诸多mTORC1的下游底物中，真核细胞翻译起始因子4E结合蛋白1（4E-binding protein 1, 4EBP1）和核糖体蛋白S6激酶（p70 ribosomal

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S6 kinases, S6K）在调控mRNA翻译、蛋白质合成和细胞增殖过程中发挥重要作用[8,10]。鸟苷三磷酸酶（GTPases）如Rag (Ras-related GTP-binding protein)和Rheb (Ras homolog enriched in brain)对于营养信号的转导和mTORC1的激活至关重要[11–13]。胞外细胞生长因子通过细胞表面受体、Akt、TSC (Tuberous sclerosis proteins)和Rheb的信号级联转导，将生长信号传递至mTORC1 [8]。mTORC1的充分激活需要其被定位至溶酶体表面，当营养物质特别是氨基酸充足时，GTP负载的Rag GTPases可以将mTORC1募集到溶酶体表面[12–14]。

近年来，越来越多的氨基酸感知因子被揭示，它们可以识别不同的氨基酸，并通过调节Rag GTPases或mTORC1复合物的定位，调节mTORC1的活性[15–23]。SLC38A9是与氨基酸转运载体同源的溶酶体跨膜蛋白，可以感知溶酶体内的精氨酸水平，并通过非经典鸟嘌呤核苷酸交换因子（guanine nucleotide exchange factor）机制激活Rag GTPases [15,24–26]。CASTOR1/2 (cellular arginine sensor for mTORC1)通过感知细胞质中精氨酸水平调节GATOR2 (GTPase activating proteins toward Rags subcomplex 2)来影响mTORC1的活性[16–17]。SAR1B (secretion associated ras related GTPase 1b)和sestrins可以感知胞内亮氨酸水平来调控mTORC1信号通路[21]。细胞蛋氨酸可以被SAMTOR (S-adenosylmethionine sensor upstream of mTORC1)感知[23]。

除了对单个氨基酸的营养感知外，机体也能够感知细胞内整体的氨基酸丰度[27]。氨基酸的短缺会造成空载的tRNA积累，其与GCN2 (general control nonderepressible 2)的氨酰基-tRNA合成酶样结构域结合，导致真核翻译起始因子2α（eIF2α）的磷酸化，从而抑制蛋白质合成[28]。虽然这些氨基酸感知信号通路普遍存在，但是其在不同组织中的活性存在差异[29]。

### 2.2. 脂质感知

分化抗原簇36（cluster of Differentiation 36, CD36）被认为在脂质感知中发挥重要作用[2]（图1）。当脂肪酸缺乏时，CD36与Src激酶Fyn以及肝激酶B1（LKB1）形成复合物，从而抑制LKB1对腺苷酸活化蛋白激酶（AMPK）的激活。而在脂肪酸充足的条件下，脂肪酸与CD36的相互作用，促进Fyn从上述蛋白质复合物中解离，使得LKB1激活AMPK [30]。多种G蛋白偶联受体（G protein-coupled receptor, GPR）对不同类型的脂肪酸也有响应（图1）。例如，GPR40和GPR120能感知中链和长链脂肪酸，GPR41和GPR43能感知短链脂肪酸，而GPR119响应脂质衍生物的丰度[31–33]。细胞核内的脂质感受器包括肝脏X受体（LXR）、孕烷X受体（PXR）和过氧化物酶体增殖物激活受体γ（PPARγ），其可以与脂肪酸和胆固醇相互作用，调节脂质代谢相关基因的表达，如脂肪酸合成酶（FASN）、SREBP1和CD36 [34–35]。SREBP1断裂激活蛋白（SREBP1 cleavage activating protein, SCAP）可以通过与胆汁酸结合并调节SREBP1转录活性的方式感知胆固醇[36]。肉碱棕榈酰转移酶1（carnitine

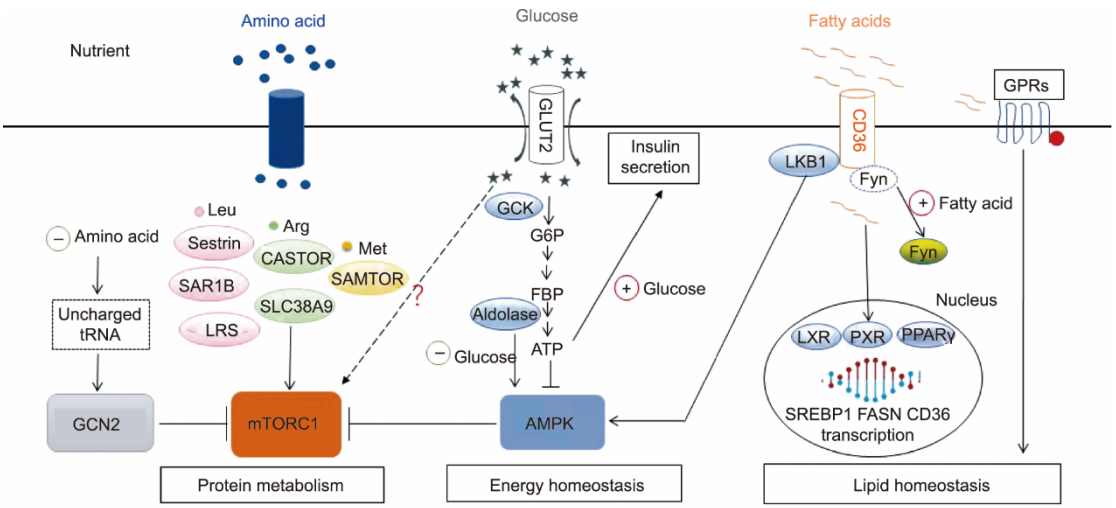


**图1.** 主要的营养感知信号通路。tRNA：转运RNA；GCN2：general control nonderepressible 2；Leu：亮氨酸；Arg：精氨酸；Met：蛋氨酸；SAR1B：secretion associated ras related GTPase 1b；LRS：亮氨酸tRNA合成酶1；CASTOR：cytosolic arginine sensor for mTORC1；SLC38A9：solute carrier family 38 member 9；SAMTOR：S-adenosylmethionine sensor upstream of mTORC1；GLUT2：2型葡萄糖转运蛋白；GCK：葡萄糖激酶；G6P：葡萄糖6-磷酸；FBP：1,6-二磷酸果糖；ATP：三磷酸腺苷；AMPK：腺苷酸活化蛋白激酶；CD36：分化抗原簇36；LKB1：肝激酶B1；Fyn：Src family tyrosine kinase；LXR：liver X receptor；PXR：pregnane X receptor；PPARγ：过氧化物酶体增殖物-活化受体γ；SREBP1：固醇调节元件结合转录因子1；FASN：脂肪酸合成酶；GPRs：G蛋白偶联受体。

palmitoyltransferase-1, CPT-1）能调节长链脂肪酰基辅酶A（long-chain fatty acyl-CoA, LCFA-CoA）进入线粒体进行β氧化，同时CPT-1在大脑、肝脏、胰腺和肌肉等不同组织中参与调控胰岛素抵抗、胰岛素分泌和食欲调控等进程[37]。

### 2.3. 葡萄糖感知

葡萄糖可在胰岛、肝脏、肌肉、下丘脑和脂肪等多种组织中被感知，而且该过程受激素和代谢中间产物的调节。葡萄糖代谢和信号转导具有组织特异性，并且也会受到组织营养状况的影响[38]。葡萄糖利用的第一步是葡萄糖激酶（glucokinase, GCK）将葡萄糖磷酸化，GCK同时也是葡萄糖的感受器[2]（图1）。与其他己糖激酶相比，GCK与葡萄糖的亲和力较低，并且仅在葡萄糖充足的条件下具有活性[39]。GCK在代谢活跃的肝脏中高度表达[40]，特定的表达模式使得GCK催化产生的葡萄糖-6-磷酸（G6P）可以根据代谢需求进入糖酵解或糖原合成过程（即用于产生或储存能量）[2]。GCK主要感知的是细胞内的葡萄糖，而细胞膜定位的2型葡萄糖转运蛋白（glucose transporter 2, GLUT2）可以感知细胞外的葡萄糖水平。与GCK类似，GLUT2对葡萄糖的亲和力相对较低，仅在高血糖的条件下起到转运葡萄糖的作用。此外，GLUT2可以双向转运葡萄糖[41–42]。因此，GLUT2仅在瞬时高血糖的情况下介导葡萄糖的输入，而在肝内葡萄糖水平较高时介导葡萄糖的输出，这使得GLUT2对维持葡萄糖的稳态尤为关键[2]。GLUT2在多种组织中都有表达，其中胰腺β细胞中的GLUT2对于葡萄糖刺激的胰岛素分泌至关重要。在神经系统中，GLUT2介导的葡萄糖感知能够控制进食和体温调节[41]。

胰岛素和胰高血糖素是控制血糖的两种激素。葡萄糖摄入的增加使得β细胞内三磷酸腺苷（ATP）的水平升高，随之而来的是膜钾通道的关闭和膜去极化，从而导致瞬时细胞内钙脉冲促进胰岛素分泌[43]。钠/葡萄糖协同转运蛋白1（sodium-glucose luminal transporter-1, SGLT1）是肠内分泌细胞转运葡萄糖的载体，并通过刺激胰高血糖素样肽-1（glucagon-like peptide-1, GLP-1）等肠道激素的分泌启动随后的信号传导[44]。肠内分泌细胞上的味觉受体T1R2-T1R3异二聚体也可以感知葡萄糖，能通过促进肠促生长素的分泌改善机体对血糖和血脂的控制[45]。葡萄糖水平也可以被AMPK和mTORC1两种关键的代谢调控信号通路间接感知。例如，醛缩酶可以感知葡萄糖低水平下的代谢中间体果糖-1,6-二磷酸（fructose-1,6-bisphosphate, FBP）激活AMPK信号通路[46]。此外，葡萄糖也可以调节Rag GTPases活性和mTORC1激活，但机制尚不清楚[47]。

## 3. 哺乳动物生长和疾病中的营养感知调控

营养感知信号通路，尤其是mTORC1信号通路，可以整合外界营养素和环境信息来调控机体的生长和健康。营养感知信号通路的失调会导致癌症、心血管疾病和神经退化等病变的发生[48–50]。mTORC1活性的缺乏会导致早发性肌肉疾病，并阻碍小鼠的生长[51]。越来越多的证据表明，mTORC1也参与调节免疫反应，如促进T细胞、B细胞和抗原呈递细胞的分化、活化和功能发挥[52–53]。此外，mTORC1信号通路的激活能促进干细胞和祖细胞的生长和增殖，并且能控制多能干细胞群的分化[54–55]。值得注意的是，mTORC1在肠上皮损伤后修复过程中，参与对多个肠上皮细胞系的调控，能够激活肠道干细胞和祖细胞[56–58]。以上证据充分说明了解析营养感知并以其为靶点进行干预对动物生长、免疫和健康等具有重要意义。

## 4. 动物营养学中的营养感知研究

### 4.1. 陆生养殖动物的营养感知

许多体内外的研究已经阐明了营养感知对养殖动物的重要性。大多数营养感知相关的分子及功能在养殖动物中高度保守[59]，例如，蛋氨酸、亮氨酸、精氨酸及一些其他氨基酸均可激活奶牛、猪和鹌鹑等养殖动物体外培养细胞系的mTORC1信号通路[60–62]。在泌乳奶牛和仔猪中的体外实验研究表明，支链氨基酸能够激活机体的mTORC1信号通路[63]。长链脂肪酸能够促进猪回肠组织释放GLP-1和GLP-2 [64]，而亚油酸的摄入与肉鸡骨骼肌中CD36的表达水平密切相关[65]。研究表明猪上皮腹泻病毒的感染与磷脂酰肌醇3-激酶-蛋白激酶B（PKB）-mTORC1信号通路有关[66]。膳食中补充亮氨酸可以减轻断奶仔猪感染猪轮状病毒引起的空肠黏膜黏蛋白分泌减少的症状[67]。仔猪断奶期间出现的肠绒毛变短及肠功能紊乱通常伴随着mTORC1活性的降低[68]。膳食中补充谷氨酸可以通过激活mTORC1信号通路，减轻断奶仔猪由脂多糖引起的肠道损伤和肠炎问题[69]。mTORC1的激活剂如支链氨基酸等也被发现可以促进断奶仔猪的肌肉生长[70–71]。

肠道中的营养感知系统可以将机体的营养状态传输至中枢神经系统，在调节猪的摄食行为方面发挥着重要作用[59]。仔猪的饮食中一般通过添加人工甜味剂来减少其断

奶后的肠道疾病，并促进仔猪的生长。近期研究表明人工甜味剂是通过增强钠-葡萄糖共转运载体1（SGLT1）的活性以及葡萄糖的吸收发挥作用[72]。味觉受体和肠道中的营养感知受体在鸡的摄食和食欲调控方面也发挥着关键作用[73]。

4.2. 水产养殖动物的营养感知

近年来，水产养殖产业开始越来越关注营养感知[3,6]。鱼类调控生长、摄食和代谢的机制与其他脊椎动物相同。mTORC1、PPARs以及AMPK等营养感知信号通路在鱼类中也高度保守[4,74–75]。尽管如此，鱼类的营养感知也有其独特之处。例如，作为变温动物，鱼类通过促进脂质分解代谢和自噬来抵抗低温，在这一过程中需要CPT-1和mTORC1等营养感知通路的参与[76]。此外，哺乳动物和鱼类中PPARα都是调控脂质分解代谢的关键通路，在尼罗罗非鱼（*Oreochromis niloticus*）中高脂饮食并不能激活PPARα，而在哺乳动物中高脂饮食可以将其激活并促进脂质分解。这一发现表明，从进化的角度来看，鱼类应对高能量饮食的自我保护机制尚未完善[77]。鱼类的多种组织中都存在餐后营养感知机制，如肠道、肝脏、胰腺、肌肉和大脑（下丘脑）等[3]。营养感知系统可以通过直接感知营养素或间接感知代谢中间产物来对机体的营养状态作出反应。

消化酶、内分泌肽和激素都会对摄食行为产生影响。下丘脑是一个营养感知信号整合中心，可以通过厌食和促食神经肽来调节食欲[6]。中枢神经系统的营养感知与外周神经系统相协调，通过分泌的神经肽和激素调节器官的代谢活动[78]。早期研究表明，mTORC1活性与摄食行为相关，并可以调节包括蛋白质合成、糖酵解、糖异生、脂肪合成在内的多种代谢进程[79–80]。脂肪酸感受器CD36在银鱼（*Pampus argenteus*）、草鱼（*Ctenopharyngodon idella*）、大西洋鲑鱼（*Salmo salar* L.）和大黄鱼（*Larimichthys crocea*）中均有表达并受饮食调控[81–84]。研究表明PPAR信号通路的失调与尼罗罗非鱼脂肪肝的发病密切相关[85]。同样的，膳食中碳水化合物的水平也会影响葡萄糖感知分子的表达水平（如葡萄糖激酶和GLUT2）以及AMPK信号通路的活性[78,86–88]。

与陆生动物相比，鱼类饲料对蛋白质的要求更高。鱼粉作为优质的蛋白源，同时也是一种有限的自然资源，不能满足水产养殖产业可持续发展的需要[89]。用植物蛋白源代替鱼粉是水产养殖饲料行业的长期目标，我国在这方面已经做了大量科研和应用工作。然而尽管水产饲料中鱼粉的用量减少是必然趋势，也不能否认鱼粉的性能优于其他蛋白源的事实[90]。我们之前的研究结果表明，以其他蛋白源替代鱼粉饲喂大菱鲆（*Scophthalmus maximus* L.）后，大菱鲆餐后mTORC1信号通路的激活被减弱，导致其对餐后合成代谢的驱动作用也减弱[91–92]。我们通过进一步的研究表明，氨基酸不平衡[93]、植物蛋白源中的抗营养因子（如棉酚[94]、皂苷[95]和凝集素[96]）的存在，都会抑制鱼类mTORC1信号通路的激活。在多种鱼类中的研究表明，饲料中添加mTORC1激活剂，如支链氨基酸[97]、谷氨酸[98]和磷脂酸[99]，能够促进鱼类对饲料的利用和生长。我们还发现，通过增加摄食频率可以靶向调控营养感知，提高餐后营养感知系统的激活程度，使得大菱鲆的生长提高7.68%，蛋白质保留率提高4.01% [97]。

## 5. 将营养感知与动物营养相结合：下一步我们能做什么？

大量研究数据表明，营养感知在代谢和疾病调控中发挥着重要作用。目前营养感知在临床上已经有广泛的应用。例如，人们尝试各种形式的禁食、蛋白质限制以及降低膳食中某些必需氨基酸（如蛋氨酸和支链氨基酸）的水平，来选择性地调控mTORC1和AMPK信号通路活性以促进健康[100]。调控营养感知通路相关的疗法（如生长激素促分泌素）已被开发用于改善患者的认知功能[101]。相比之下，营养感知与动物营养的结合仍处于起步阶段。从我们的角度来看，为了动物营养学能更好地发展，从以下几个方向开展研究是非常必要的。

5.1. 营养感知与饲料配方的相关性研究

目前为止，大多数相关的研究都是通过体外细胞系或体内动物模型，来阐明对特定营养素感知的基本机制。然而，实际的饲料配方要复杂得多。传统意义上饲料性能是通过表型参数来评估的，如生长速率、饲料转化效率、蛋白质保留率等。阐明相关的营养感知响应机制，对于我们理解饲料性能以及进一步优化饲料配方是很有价值的。

5.2. 将营养感知与新技术结合来开展未来营养学研究

使用大剂量的同位素标记的方法测定蛋白质合成速率已有几十年的历史[102]。然而直到最近代谢通量分析（metabolic flux analysis, MFA）才成为定量代谢分析的重要工具[103]。MFA的核心概念是细胞内代谢物的同位素标记模式由代谢通量决定的，因此通过测定标记模式，我们可以定量地推断出代谢动力学。营养学研究可以利用基

因组学、转录组学、蛋白质组学和代谢组学等丰富的组学技术，来探究食物与生物系统之间的相互作用。目前利用系统生物学的方法处理基因组、mRNA、蛋白质和代谢物信息，已经收集和分析了大量数据，有助于全面了解分子调控网络。相对的这也需要对高通量信息进行分类和核实。只有我们充分了解营养感知信号通路对营养素和中间代谢产物的响应，才能知道细胞和生物体之间如何统一协作。

5.3. 定向干预营养感知，实现精准营养目标

营养感知分子，特别是mTORC1，已经被当作治疗靶点来研发新药物。因此精准营养的策略被提出来，旨在通过调控营养感知的响应，协助对癌症[104]、阿尔茨海默病[105]、唐氏综合征[106]和肌肉减少症[107]等疾病的治疗康复。营养感知也为动物营养开辟了一条新的研究途径。在餐后营养感知动力学的指导下，可以系统地进行饲料配方优化以提高产出。现在是时候将营养感知和高通量技术的理论与传统营养学方法相结合，并在精准营养指导下进行大规模的试点试验，这将为动物营养学的未来奠定基础。

5.4. 研发用于实时监测动物健康和营养状态的生物标志物和技术

mTORC1等营养感知分子具有成为生物标志物的潜力：首先这些分子的活性能反映机体营养状态并呈现剂量依赖性[92,97,108]，并且它们对肌肉蛋白沉积和免疫反应等器官特异性的功能至关重要，因此可以测定这些分子的活性以预测结果。然而目前仍需要付出大量努力来筛选和选择潜在的指示养殖动物营养和健康状态的生物标志物。我们已经见证了生物传感技术与物联网（IoT）集成的迅速发展，并实现了对养殖动物（如牛）的健康和生物福利的快速、现场、实时监测[109]。除此之外还开发了传感器来监测动物的营养状况[110]。尽管如此，仍然有必要为特定生理目的及特定的品种开发更准确、更高效的监测技术。这些数据对未来精准养殖业的发展极具价值。

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## 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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