

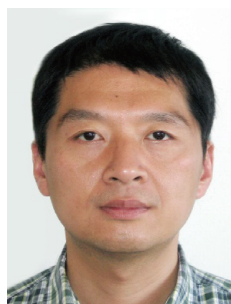
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雷群英, 新基石研究员, 现任复旦大学基础医学院院长和中国细胞生物学学会细胞代谢分会主任委员。主要聚焦营养与肿瘤代谢研究, 发现了系列代谢感知的新通路, 突破了经典的细胞代谢感知理论。首次发现乙酰辅酶A作为信号分子调控线粒体自噬, 揭示了代谢物充当信号分子, 为代谢感知调控肿瘤(细胞)命运奠定理论基础; 系统阐明了代谢感知异常通过表观遗传和翻译后修饰的新机制促进疾病发生发展; 揭示了肿瘤高度异质性的代谢内因, 提出胰腺癌的代谢起源假说; 证实代谢感知异常协同基因突变驱动肿瘤发生, 为肿瘤代谢靶向干预提供新策略。成果在*Nature*、*Nat Immunol*、*Nat Metab*、*Nat Cell Biol*、*Cancer Cell*、*Mol Cell*等发表。多次被*Nature*等杂志专题评述, 连续多次被选为中国高被引学者, 受邀在*Nat Cell Biol*、*Nat Metab*、*Mol Cell*及*J Biol Chem*等发表评/综述。主持国家重点研发计划、国家自然科学基金委重大项目、创新研究群体项目、杰出青年科学基金项目, 以及教育部基础医学学科突破先导项目等。先后获中国青年女科学家奖、上海市自然科学奖一等奖、谈家桢生命科学创新奖、吴阶平-保罗·杨森医学药理学奖、中国细胞生物学学会杰出成就奖和全国创新争先奖等荣誉。



尹森, 复旦大学附属肿瘤医院副研究员。致力于利用类器官模型、动物模型、人体肿瘤组织样本深入研究代谢感知重塑和肿瘤微环境的相互调控在肿瘤发生发展中的作用和机制, 为肿瘤代谢靶向干预和效率评估提供理论基础和重要技术手段。研究工作以(共同)通讯作者和第一作者发表在*Nat Immunol*、*Nat Metab*、*Nat Cell Biol*、*Mol Cell*、*Signal Transduct Target Ther*、*Autophagy*、*Sci China Life Sci*、*Am J Pathol*等杂志, 被*Nat Immunol*、*Mol Cell*、*Nat Rev Endocrinol*、*Nat Cell Biol*、*Am J Pathol*等杂志专题评述或选为亮点文章, 并以通讯作者在*Nat Metab*、*Nat Cell Biol*等发表评/综述。

氨基酸信号感知机制进展介绍

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摘 要: 氨基酸是生物体的关键营养物质之一。越来越多的研究证实氨基酸不仅是细胞内生物合成的重要原料, 也作为信号分子被细胞内各类感知受体结合, 调控细胞生长、自噬和迁移等各种重要细胞活动, 维持细胞稳态。氨基酸信号感知失衡会引起代谢紊乱和肿瘤发生等多种病理效应。本文综述了近年来从机制性雷帕霉素靶蛋白复合物1(mechanistic target of rapamycin complex 1, mTORC1)和一般性调控阻遏蛋白激酶2(general control nonderepressible-2, GCN2)等经典的氨基酸感知信号通路的深入探究到支链氨基酸、精氨酸等新的非经典感知机制的解析。这些研究都显示出细胞内存在时、空、量等多维层面的氨基酸感知调控网络, 显著拓宽了我们对细胞内代谢物感知的认识。这一多维氨基酸感知调控网络也亟需发展能够更精准地定量检测氨基酸等代谢物在特定时间、空间的水平及代谢物流向的技术方法, 从而全面绘制氨基酸等代谢物感知的时、空、量的多维图谱。

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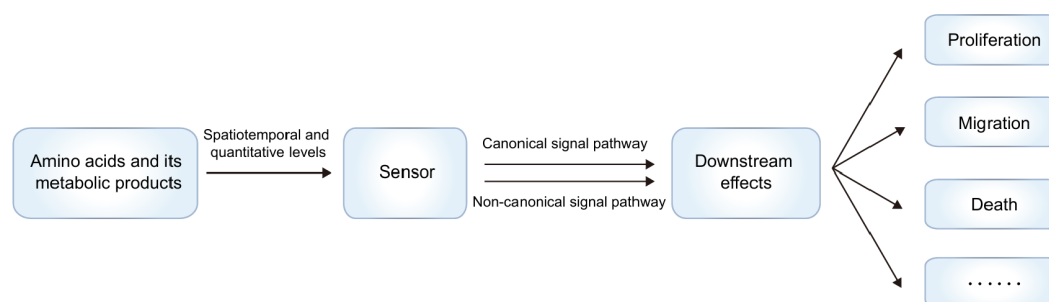
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Advances of research on amino acid sensing

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Abstract: Cell metabolism is finely regulated by intrinsic and extrinsic nutritional signals. It is noteworthy that metabolites not only serve as substrates for anabolism and products of catabolism but can also function directly as nutrient signaling molecules. They are sensed by various receptors in cells to regulate signaling pathways, facilitating the exchange of biomaterials, energy, and information between the internal and external environments of cells. This process is essential to ensure cell survival and properly maintain cellular functions. Amino acids are important nutrients for life. They not only serve as building blocks for intracellular biosynthesis but also act as signaling molecules that bind to various intracellular sensing receptors. This enables the cell to perceive extracellular and intracellular amino acid nutrient signals and convert them into physiological signals. Through the intracellular signaling network, these signals finely regulate metabolic pathways at multiple levels, including epigenetic, transcriptional, translational, and post-translational modifications, allowing the cell to adapt to the nutrient status of its internal and external environments. The amino acid sensing regulates various critical cellular activities such as growth, autophagy, and migration, thereby maintaining cellular homeostasis. Dysregulation of amino acid signal sensing can lead to metabolic disorders, tumor development, and other pathological effects. In recent years, the signaling functions of amino acids and their metabolites have attracted increasing attention. Growing evidence has confirmed that, similar to classical intracellular signal transduction via protein kinase phosphorylation of downstream molecules, protein kinase complexes such as the mechanistic target of rapamycin complex 1 (mTORC1) and general control nonderepressible-2 (GCN2) are important amino acid sensing pathways. However, an increasing number of recent studies have extended beyond these canonical metabolic sensing pathways, demonstrating the existence of multi-level amino acid sensing mechanisms within cells. This article reviews recent advances from in-depth investigations of canonical amino acid sensing pathways such as mTORC1 and GCN2 to the elucidation of new non-classical sensing mechanisms for branched-chain amino acids, arginine, and others. It reveals the presence of a multi-dimensional amino acid sensing regulatory network within cells, operating across temporal, spatial, and quantitative levels, greatly expanding our understanding of metabolite sensing in cells. To comprehensively map the temporal, spatial, and quantitative dimensions of amino acid and other metabolite sensing, there is an urgent need to develop more precise methods for quantitatively detecting the metabolite levels and their fluxes at specific phases and tissue- and subcellular-locations.



Key words: cell metabolism; metabolite sensing; amino acid; signaling molecule

细胞代谢是最基本的生命活动之一。细胞内由代谢酶和代谢物组成的复杂代谢通路精确执行物质和能量合成或降解,应对细胞内外营养状况,满足细胞生长、分化、信号转导和运动等各种生命活动的需求。细胞代谢受到细胞内外营养信号的精细调控。

值得关注的是,代谢物不仅作为合成代谢的底物和分解代谢的产物,还可以直接作为营养信号分子,被细胞内受体感知,调控细胞内的信号通路,完成细胞与内外环境间物质、能量和信息的有机交流,对保证细胞存活、维持细胞正常功能具有重要意义^[1,2]。

氨基酸是维持生命所必需的营养物,它们不仅是合成蛋白质的基本原料,还通过合成与分解代谢,为体内能量和物质合成提供碳源和氮源,广泛调控表观遗传、DNA复制、激素合成、氧气运输、氧化应激、细胞增殖,从而影响机体的内分泌、神经、免疫等系统的重要生理功能,其代谢失衡将引发糖尿病、肿瘤等多种疾病。近些年来,氨基酸及其代谢物的信号分子功能日益受到重视^[3]。越来越多的研究证实,细胞内氨基酸的波动,包括不同浓度,不同时间、不同亚细胞区域的动态变化信号能被细胞所感知,转变为生理信号,通过细胞内信号网络,从表观、转录、翻译以及翻译后修饰等多个层面,精细调控细胞代谢通路开关,使细胞适应内外环境的营养状态,维持细胞的正常功能和机体稳态。氨基酸及其代谢物的信号异常,也可被细胞感知,造成细胞代谢和生长失衡,导致慢性炎症和肿瘤等疾病的发生发展^[4,5]。与经典的依赖蛋白激酶磷酸化下游蛋白分子转导细胞内信号类似,蛋白激酶复合物机制性雷帕霉素靶蛋白复合物1(mechanistic target of rapamycin complex 1, mTORC1)和蛋白激酶一般性调控阻遏蛋白激酶2(general control nonderepressible-2, GCN2)介导的信号通路是被广泛研究的细胞内氨基酸信号感知通路^[6-9]。然而,目前越来越多的研究发现突破了这些经典代谢感知通路,证实细胞内存在多层次的氨基酸感知方式。

1 经典的氨基酸感知信号通路

1.1 mTORC1介导的氨基酸感知通路

mTORC1通路是细胞内与代谢密切相关的核心信号通路,通过感知并整合细胞内外营养和生长因子信号,作用于下游效应分子,如磷酸化激活核糖体蛋白S6激酶1(ribosomal protein S6 kinase 1, S6K1)和真核起始因子4E结合蛋白1(eukaryotic initiation factor 4E binding protein 1, 4E-BP1)来促进翻译和蛋白质合成,而磷酸化unc-51样自噬活化激酶1(unc-51 like autophagy activating kinase 1, ULK1)和转录因子EB(transcription factor EB, TFEB)抑制了细胞自噬和溶酶体生成,造成细胞内的合成代谢增强,分解代谢受到抑制^[10]。mTORC1复合体的核心组成包括具有丝/苏氨酸蛋白激酶活性的mTOR、负责招募底物以及稳定mTORC1复合体的mTOR调节相关蛋白(regulatory-associated protein of mTOR, Raptor)以及维持mTOR蛋白激酶活性的哺乳动物致死性Sec13

蛋白8(mammalian lethal with Sec13 protein 8, mLST8)。三者组成的异源三聚体通过二聚化,构成mTORC1核心^[10,11]。此外,某些分子,如含DEP结构域的mTOR相互作用蛋白(DEP domain-containing mTOR interacting protein, DEPTOR)和脯氨酸富集的40千道尔顿AKT底物(proline-rich Akt substrate of 40 kDa, PRAS40)等作为mTORC1非核心组分,负调控mTORC1信号通路^[12,13]。细胞中mTORC1对氨基酸丰度信号的感知主要通过小三磷酸鸟苷水解酶(guanosine triphosphatase, GTPases)家族的Rag蛋白与Ragulator/Lamtor复合物相互作用,使其定位在溶酶体外膜^[14,15]。当细胞中氨基酸丰度高时,Rag与mTORC1结合,将其招募至溶酶体外膜,由脑富集Ras同源(Ras homolog enriched in brain, RHEB)GTPase激活^[15,16]。相反地,氨基酸丰度低时,Rag保持非活化形式,mTORC1滞留在细胞质中,处于失活状态^[14-16]。GTPase活化蛋白(GTPase activating protein, GAP)协助GTPase促进GTP水解生成GDP,导致GTPase活性抑制。在Rag GTPase的GAP(GTPase activating proteins toward Rags, GATOR)蛋白复合体中,GATOR1阻止Rag活化mTORC1^[17,18]。而GATOR蛋白复合体的另一个成员GATOR2则抑制GATOR1^[19,20]。此外,溶酶体膜上的蛋白复合物KICSTOR结合GATOR1,并使其定位在溶酶体膜上,维持GATOR1的负调控功能(图1)^[21,22]。近些年的研究发现氨基酸激活mTORC1信号通路的机制可分为Rag GTPases依赖和非依赖性^[23]。也有报道溶酶体定位的mTORC1信号通路主要感知溶酶体内或其外流的氨基酸水平,而感知外源氨基酸还可以通过非溶酶体定位、不依赖Rag GTPase的mTORC1信号通路^[24]。

近十年来的研究发现了支链氨基酸(branched chain amino acid, BCAA)、甲硫氨酸和精氨酸被经典的mTORC1信号通路感知的机制。BCAA是必需氨基酸,其中亮氨酸(leucine, Leu)分别直接结合细胞浆中的应激诱导蛋白Sestrin2、SAR1B GTPase和亮氨酸-tRNA合成酶(leucyl-tRNA synthetase, LARS1),激活mTORC1信号通路^[25-28]。作为亮氨酸感知受体,当亮氨酸缺乏时,Sestrin2和SAR1B均可与GATOR2相互作用,并抑制GATOR2^[26,29,30]。而当胞浆中亮氨酸丰度高时,结合了亮氨酸的Sestrin2/SAR1B与GATOR2解离,被释放的GATOR2

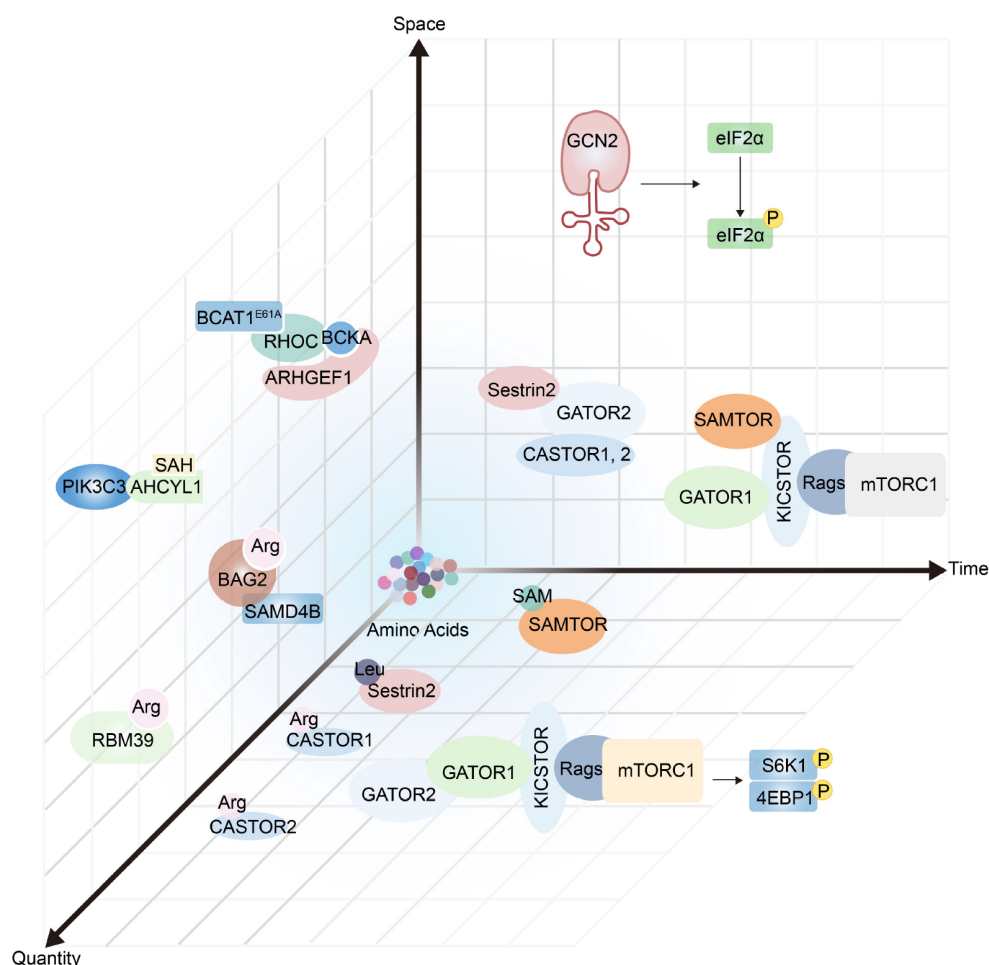


图1 氨基酸信号感知机制示意图

从经典的蛋白激酶复合物机制性雷帕霉素靶蛋白复合物1和蛋白激酶一般性调控阻遏蛋白激酶2介导的氨基酸感知信号通路,到新近发现的非经典氨基酸感知受体,细胞内的氨基酸作为信号分子被感知时,受到不同时间、不同空间(包括亚细胞定位和组织)和不同丰度等多维层面的精细网络调控,在细胞稳态维持和各类生理和病理过程中发挥关键作用。Amino Acids:氨基酸; mTORC1:机制性雷帕霉素靶蛋白复合物1;GATOR: 靶向Rags的GTPase活化蛋白;S6K1:核糖体蛋白S6激酶1;4E-BP1:真核起始因子4E结合蛋白1;GCN2:一般性调控阻遏蛋白激酶2;eIF2 α :真核起始因子-2 α ;Leu:亮氨酸;SAM:腺苷甲硫氨酸;SAMTOR:mTORC1上游SAM感受器;Arg:精氨酸;CASTOR1:胞浆mTORC1精氨酸感受器;BAG2:Bcl2相关抗凋亡基因2;SAMD4B:不育ALPHA基序结构域蛋白4B;RBM39:RNA结合基序蛋白39;BCAT1^{E61A}:第61位氨基酸由谷氨酸突变为丙氨酸的支链氨基酸转氨酶1;BCKA:支链酮酸;RhoC:Ras同源基因家族成员C;ARHGEF1:Rho鸟嘌呤核苷酸交换因子1;SAH:腺苷高半胱氨酸;AHCYL1:类腺苷高半胱氨酸水解酶1;PIK3C3:磷脂酰肌醇3-激酶3型催化亚基;Time:时间;Space:空间;Quantity:量度。

Figure 1 Schematic diagram of amino acid sensing mechanisms

Intracellular amino acids act as signaling molecules, which are sensed by both canonical amino acid sensing pathways such as the mechanistic target of rapamycin complex 1 and general control nonderepressible 2 protein kinase and the non-canonical amino acid sensing receptors discovered recently, and fine-tuned at multiple levels involving temporal, spatial, as well as quantitative dimensions. The amino acid sensing network plays a critical role in cellular homeostasis maintenance and various physiological and pathological processes. mTORC1: mechanistic target of rapamycin complex 1; GATOR: GTPase activating proteins toward Rags; S6K1: ribosomal protein S6 kinase 1; 4E-BP1: eukaryotic initiation factor 4E binding protein 1; GCN2: general control nonderepressible-2; eIF2 α : eukaryotic initiation factor-2 α ; Leu: leucine; SAM: S-adenosylmethionine; SAMTOR: S-adenosylmethionine sensor upstream of mTORC1; Arg: arginine; CASTOR1: cellular arginine sensor for mTORC1; BAG2: Bcl2-associated athanogene 2; SAMD4B: sterile alpha motif domain containing 4B; RBM39: RNA-binding motif protein 39; BCAT1^{E61A}: branched-chain amino acid transaminase 1 with substitution mutation from glutamate (E) to alanine (A) at 61st residue; BCKA: branched-chain α -ketoacid; RhoC: Ras homolog gene family member C; ARHGEF1: Rho guanine nucleotide exchange factor 1; SAH: S-adenosyl-L-homocysteine; AHCYL1: adenosylhomocysteinase like 1; PIK3C3: phosphatidylinositol 3-kinase catalytic subunit type 3.

结合并抑制GATOR1,从而激活mTORC1信号通路^[25,26]。亮氨酸结合LARS1改变其构象,使LARS1与RagD结合,活化mTORC1信号通路,并且LARS1的底物之一三磷酸腺苷(adenosine triphosphate, ATP)增强亮氨酸与LARS1之间的结合。LARS1催化ATP的产物单磷酸腺苷(adenosine monophosphate, AMP)结合亮氨酸,生成Leu-AMP,阻止LARS1结合亮氨酸和RagD,负调控mTORC1信号通路,与此同时,LARS1结合tRNA,并促进亮氨酰-tRNA生成,参与蛋白质合成^[31]。LARS1感知亮氨酸还受到葡萄糖的调控。葡萄糖缺乏时,LARS1上O连接的N乙酰葡萄糖胺修饰水平升高,抑制LARS1与RagD结合^[32]。也有研究发现亮氨酸促进LARS1结合并活化磷酸肌醇3-激酶家族成员VPS34,引起细胞浆中磷脂酰肌醇三磷酸(phosphatidylinositol 3-phosphate, PtdIns3P)增加,进而通过磷脂酶D(phospholipase D, PLD)激活mTORC1信号通路^[33]。而VPS34-PLD通路还可能参与介导了亮氨酸信号引起的内质网中钙离子释放活化mTORC1^[34],此过程中G蛋白偶联受体(G protein-coupled receptor, GPCR)也可能是潜在的亮氨酸感知受体^[35]。有趣的是,细胞感知亮氨酸丰度的另一种形式是通过其代谢产物乙酰辅酶A(acetyl coenzyme A, Acetyl-CoA)。研究发现亮氨酸来源的Acetyl CoA提供乙酰基团,在赖氨酸乙酰转移酶EP300作用下,催化Raptor发生乙酰化修饰。破坏Raptor的乙酰化修饰,并不影响mTORC1复合体的组装,但抑制了mTORC1与Rag的相互作用,从而抑制mTORC1信号通路。在接受禁食处理的小鼠神经和肌肉组织中也能观察到Acetyl-CoA水平和Raptor乙酰化水平的显著下降以及mTORC1信号通路被抑制。值得注意的是,通过Acetyl-CoA调控mTORC1信号来感知细胞中亮氨酸丰度存在组织特异性。该机制可以在神经细胞中发生,但鼠胚成纤维细胞和肾上皮细胞在缺乏亮氨酸时,细胞中Acetyl-CoA水平仍很高,提示其他营养来源、如葡萄糖、脂肪酸或其他氨基酸是这些细胞中Acetyl-CoA的主要来源,因此,这些细胞不依赖于亮氨酸-Acetyl-CoA通路调控mTORC1信号。这体现了氨基酸感知的组织空间特异性^[36,37]。

不同于BCAA直接结合感知受体,甲硫氨酸在体内被甲硫氨酸腺苷转移酶(methionine adenosyltransferase, MAT)催化生成腺苷甲硫氨酸

(S-adenosylmethionine, SAM)^[38,39]。SAM不仅是细胞内甲基化反应的主要供体,也是细胞感知甲硫氨酸水平的信号分子。mTORC1上游SAM感受器(S-adenosylmethionine sensor upstream of mTORC1, SAMTOR)结合KICSTOR复合物中的SZT2亚基,与KICSTOR-GATOR1形成复合体,抑制mTORC1的活化,而SAM结合在SAMTOR的甲基转移酶结构域,阻止SAMTOR与SZT2的结合,造成SAMTOR与KICSTOR-GATOR1复合体的解离,活化mTORC1^[22,40]。因此,当细胞内缺乏甲硫氨酸时,SAM水平降低,SAMTOR与GATOR1-KICSTOR的结合增强,抑制了mTORC1^[40,41]。近期的一项研究揭示,当细胞内甲硫氨酸充足时,SAM结合SAMTOR,阻止其与GATOR1的结合,同时促进蛋白精氨酸甲基转移酶1(protein arginine methyltransferase 1, PRMT1)与GATOR1结合,使GATOR1的催化亚基NPRL2发生甲基化修饰,抑制其GAP活性,激活mTORC1^[42]。SAM的感知也存在物种差异。在果蝇中,SAM与甲基转移酶Unmet结合,破坏其与GATOR2的结合,激活GATOR2-mTORC1信号通路^[43]。值得注意的是,尽管Unmet在果蝇和人之间存在保守性,但Unmet并不能结合人的GATOR2,显示SAM-Unmet-GATOR2介导的甲硫氨酸感知有种属特异性。有趣的是,从酵母到脊椎动物的Unmet都保持了甲基转移酶活性。而在果蝇中,Unmet获得了感知SAM的功能。这可能是由于在物种演化过程中,不同物种利用的饮食营养存在差异,使其获得了特定的感知模式。这种营养物感知受体物种差异,而mTOR核心复合物相对保守的特征,体现了演化过程中物种适应不同饮食营养的灵活性^[43]。此外,GPCR可以感知多种氨基酸信号。有报道显示在肌细胞中,甲硫氨酸可以通过GPCR-钙离子信号调控mTORC1^[44,45]。

与BCAA和甲硫氨酸感知相比,精氨酸感知机制的研究进一步拓展了我们对细胞内代谢物感知的空间区室化和量化效应的理解。精氨酸虽是一种非必需氨基酸,但在特定生理病理条件下,如孕期和肿瘤等,内源合成的精氨酸不能满足需求,需要外源补充^[46,47]。因此,精氨酸也是一种半必需氨基酸。精氨酸作为信号分子被感知的机制也有较多的研究,有多个精氨酸感受器参与调控mTORC1信号通路。其中,位于胞浆的mTORC1精氨酸感受器

(cellular arginine sensor for mTORC1, CASTOR1)与亮氨酸感受器Sestrin2一样,均作用于GATOR2^[48]。CASTOR1同型二聚体的两个亚基在缺乏精氨酸时,均与GATOR2的MIOS亚基结合以抑制GATOR2,维持GATOR1对mTORC1的抑制^[49]。精氨酸结合在CASTOR1的ACT结构域时,变构调控邻近的GATOR2结合位点,使CASTOR1与GATOR2解离,从而激活下游mTORC1信号^[50]。值得注意的是,CASTOR1与精氨酸的解离常数约为5~35 $\mu\text{mol/L}$,细胞内精氨酸浓度可达500 $\mu\text{mol/L}$ 以上。而精氨酸浓度会受到禁食与饥饿以及不同生理病理和疾病治疗干预的影响,有较大的波动。近期的一项研究报道了CASTOR1主要通过感知低精氨酸浓度(细胞培养环境中的精氨酸低于400 $\mu\text{mol/L}$)激活mTORC1,而CASTOR1的同源蛋白CASTOR2虽然与精氨酸结合力弱,解离常数超过200 $\mu\text{mol/L}$,可在体内高精氨酸环境中(细胞培养环境中的精氨酸高于600 $\mu\text{mol/L}$)负责精氨酸感知,通过GATOR2激活mTORC1^[51]。这些研究体现了细胞应对体内精氨酸水平波动时的分时相调控。另一个已知的精氨酸感知受体是位于溶酶体膜上的跨膜蛋白溶质载体(solute carrier, SLC)38A9。SLC38A9感知溶酶体内的精氨酸量化水平,从而结合并转运溶酶体内的精氨酸进入细胞质。溶酶体内的精氨酸通过促进SLC38A9与Rag-Ragulator的相互作用,增强mTORC1信号^[52-54]。SLC38A9不仅是精氨酸转运蛋白,还是溶酶体内多种氨基酸的转运蛋白,特别是将精氨酸从溶酶体转运至细胞浆,通过精氨酸感知间接调控mTORC1信号通路^[54]。此外,跨膜蛋白4L6家族成员5(transmembrane 4L six family member 5, TM4SF5)在精氨酸充足时从细胞膜转位至溶酶体膜上,与mTOR和SLC38A9形成复合体,并通过其溶酶体腔内段结合精氨酸,感知溶酶体内的精氨酸水平,活化mTORC1通路^[55]。精氨酸还可以参与生长因子对mTORC1信号通路的调控。该机制主要是精氨酸阻止结节性硬化症蛋白2(tuberous sclerosis complex 2, TSC2)的溶酶体定位,解除其对Rheb GTPases的抑制^[56,57]。

上述研究主要揭示了依赖于Rag GTPase-mTORC1通路的氨基酸感知机制。另一方面,天冬酰胺和谷氨酰胺可通过不依赖于Rag GTPase的机制被感知,调控mTORC1^[23]。在Rag GTPase缺失的

细胞中,天冬酰胺和谷氨酰胺均可诱导mTORC1定位于溶酶体,促进其活化,该效应依赖于ADP-核糖基化因子(ADP-ribosylation factor, ARF)^[58],此外,在发生巨胞饮的细胞中,溶酶体上天冬酰胺和谷氨酰胺的转运蛋白SNAT7以不依赖于Rag GTPase的方式,与mTORC1相互作用,介导mTORC1在溶酶体的定位及活化^[59]。在酵母中,磷脂酰肌醇三磷酸结合蛋白2(PtdIns3P binding protein 2, Pib2)位于滤泡(类似溶酶体)膜上,与mTORC1相互作用,以独立于Gtr(对应于Rag GTPase)的方式调控mTORC1;谷氨酰胺和半胱氨酸均可直接结合Pib2,活化mTORC1^[60-62]。与不依赖Rag GTPase调控mTORC1通路的机制不同,溶酶体内半胱氨酸外排与谷氨酰胺分解生成 α -酮戊二酸则均能通过依赖Rag GTPase的方式激活mTORC1^[58,63-65],表明细胞对代谢物感知的复杂性和高度可塑性。值得注意的是,氨基酸信号激活mTORC1通路有快速短暂和慢速持续两个时相。几乎所有氨基酸均可快速短暂地活化mTORC1,而只有特定的氨基酸,如谷氨酰胺,能够诱导慢速持续的mTORC1活性状态。

1.2 GCN2介导的氨基酸感知通路

通常,细胞内高丰度氨基酸激活mTORC1促进合成代谢,而GCN2信号通路感知氨基酸缺乏,促进分解代谢。蛋白质翻译时,氨基酸结合相应的转运RNA(transfer RNA, tRNA),参与核糖体的组装和蛋白质翻译。氨基酸缺乏,甚至单个氨基酸的缺乏,会造成未结合氨基酸的tRNA在细胞中积累并与GCN2结合,引起GCN2的构象变化和自磷酸化,从而激活其丝/苏氨酸激酶活性,磷酸化下游底物^[66,67]。也有新的研究报道了依赖于核糖体碰撞的GCN2活化新机制。氨基酸缺乏等应激信号引起的核糖体碰撞,相继招募GCN1和GCN2,活化GCN2^[68]。翻译起始因子真核起始因子-2 α (eukaryotic initiation factor-2 α , eIF2 α)作为GCN2的底物之一,被磷酸化后,阻止了eIF2 α 与起始甲硫氨酸-tRNA和GTP形成三元复合物,抑制细胞内普通蛋白质合成的帽依赖翻译途径,减少细胞能量和营养需求(图1),同时促进活化转录因子4(activating transcription factor 4, ATF4)一类应激蛋白的非帽依赖翻译,ATF4合成增加进入细胞核,调控细胞应激反应蛋白的基因表达,使细胞适应应激,如激活细胞自噬^[69,70]。

mTORC1和GCN2信号通路作为响应细胞内氨基酸丰度/量化水平信号的两个经典通路,彼此之间也存在相互串扰,协调细胞内的营养应激。当氨基酸缺乏时,活化的GCN2磷酸化S期蛋白激酶相关蛋白1(S-phase kinase-associated protein 1,SKP1)-滞蛋白1(cullin 1,CUL1)-F-盒蛋白(F-box protein,FBXO)组成的E3连接酶复合物中的底物受体蛋白-F-盒蛋白22(F-box protein 22,FBXO22)的127位苏氨酸,阻止FBXO22进入细胞核,使其滞留在细胞浆。胞浆中的FBXO22促进mTOR的2066位赖氨酸发生K-27链接的泛素化修饰,从而阻止mTORC1募集下游底物,抑制mTORC1信号通路^[71]。有趣的是,谷氨酰胺的缺乏也可以通过GCN2调控mTORC1^[72]。谷氨酰胺是天冬酰胺的氨基供体,并且天冬酰胺在细胞中很少进行下一步的代谢。细胞中谷氨酰胺缺乏造成下游代谢产物天冬酰胺含量下降,激活GCN2。谷氨酰胺短期内(1小时)缺乏时,GCN2通过Rag GTPase依赖方式抑制mTORC1信号通路。Ddit4可通过TSC复合物-Rheb通路抑制mTORC1^[73]。当延长谷氨酰胺缺乏时间,活化的GCN2在转录水平上调Ddit4的表达,从而通过Rag GTPase非依赖方式抑制mTORC1信号通路。值得注意的是,除了谷氨酸、半胱氨酸和组氨酸,其他氨基酸缺乏均可在短时间内通过GCN2抑制mTORC1^[72]。以上研究显示,GCN2结合mTORC1能更广谱而精细地感知细胞内氨基酸的丰度。

有研究发现,正常蛋白饮食时,肠道上皮细胞中GCN2的活性被抑制,脆性X智力迟钝蛋白核相互作用蛋白1(nuclear fragile X mental retardation-interacting protein 1,NUFIP1)被细胞周期素依赖蛋白激酶9磷酸化,招募共济失调-毛细血管扩张和Rad3相关激酶(ataxia telangiectasia and Rad3-related kinase,ATR)与ATR相互作用蛋白(ATR-interacting protein,ATRIP)到DNA损伤位点,维持细胞内正常的DNA损伤反应(DNA damage response,DDR),保证肠道上皮的稳态。低蛋白饮食能够加重肠炎反应,其机制是氨基酸缺乏激活GCN2信号通路,下调NUFIP1,破坏DDR,诱发细胞坏死性凋亡。值得注意的是,在该调控途径中,GCN2并不通过mTORC1影响NUFIP1介导的DDR和肠道上皮坏死性凋亡^[4]。这一结果显示GCN2和mTORC1信号通路的串话存在组织和细胞异质性。

1.3 神经递质受体介导的氨基酸感知通路

有些氨基酸,包括天冬氨酸、谷氨酸和甘氨酸等,与细胞表面受体结合后发挥神经递质功能,调控细胞内信号与功能。如离子通道型受体N-甲基-D-天[门]冬氨酸(N-methyl-D-aspartate,NMDA)受体可以被天冬氨酸、谷氨酸和甘氨酸结合活化。天冬氨酸结合肿瘤细胞表面该型受体中的谷氨酸离子通道受体NMDA型亚基2D(glutamate ionotropic receptor NMDA type subunit 2D,GRIN2D),通过细胞内环磷腺苷效应元件结合蛋白(cAMP-response element binding protein,CREB)上调脱氧羟腐胺羟化酶(deoxyhypusine hydroxylase,DOHH)基因表达,增强真核起始因子5A(eukaryotic initiation factor 5A,eIF5A)的羟脯氨酸化,调控下游翻译,激活转化生长因子- β (transforming growth factor- β ,TGF- β)信号通路^[74]。除了离子通道型受体,这类神经递质氨基酸的受体还包括G蛋白偶联受体家族成员中的代谢型受体,其被激活后,传递细胞内信号^[75]。

2 非经典的氨基酸感知信号通路

近年来的研究显示,除了mTORC1和GCN2经典的氨基酸感知信号通路,细胞内还存在非经典的感知机制,这些发现进一步丰富了细胞内氨基酸感知的多样性,并拓宽了我们对于细胞适应各种内外应激条件的精细调控机制的认识。

2.1 支链氨基酸的非经典感知机制

血清等组织中BCAA水平升高与肥胖密切相关,在肥胖人群中血清BCAA水平升高约2倍^[76,77]。肥胖主要表现为白色脂肪组织的过度增长。BCAA代谢的第一步是通过支链氨基酸转氨酶(branched-chain amino acid transaminase,BCAT)催化生成支链酮酸(branched-chain α -ketoacid,BCKA)。在脂肪组织中敲除*Bcat2*,阻断其中的BCAA代谢,可以使小鼠血清BCAA升高2~3倍。脂肪组织条件性敲除*Bcat2*并未引起脂肪组织中mTORC1信号升高^[78],而全身敲除*Bcat2*可活化mTORC1。值得注意的是,全身敲除*Bcat2*的小鼠血清中BCAA升高15~30倍,远远超过正常生理病理条件下BCAA升高的幅度。与之一致,在脂肪细胞中敲除*Bcat2*也能造成细胞中BCAA水平大幅升高,激活mTORC1信号通路。此外,在高脂和高BCAA饮食喂养的小鼠肌肉组织中,

可以观察到mTOR磷酸化水平升高^[79],提示BCAA感知在不同组织中存在差异性。有趣的是,BCAA的代谢产物Acetyl-CoA是脂肪细胞中Acetyl-CoA的重要来源之一,并且发挥信号分子作用:乙酰化修饰转录共调节因子正调节结构域锌指蛋白16(positive regulatory domain zinc finger protein 16, PRDM16),破坏PRDM16与转录因子过氧化物酶体增殖物激活受体 γ (peroxisome proliferator-activated receptor γ , PPAR γ)的结合,抑制脂肪细胞棕色化和产热,维持白色脂肪组织的稳态。

BCAA的直接分解产物BCKA被支链酮酸脱氢酶(branched-chain α -keto acid dehydrogenase, BCKDH)复合体氧化分解,该反应为BCAA分解代谢中不可逆的限速步骤。BCAT2和BCKDH能够形成动态的区室化的代谢中间体,加速BCAT2催化转氨生成的BCKA经BCKDH氧化分解,避免BCAA和BCKA的蓄积^[80,81]。组成BCKDH复合体的亚组分E1和E2失活突变会导致BCAA和BCKA的异常蓄积,造成细胞毒性反应^[82]。近期有报道在胃癌患者中发现BCAT1的第61位氨基酸由谷氨酸突变为丙氨酸,BCAT1^{E61A}催化BCAA的酶活性显著增强^[83]。在携带该突变的患者血清、突变细胞和敲入该突变的转基因动物模型血清中,BCAA和BCKA浓度也显著升高。该研究还发现敲入该突变的转基因动物的肝和胃组织中mTORC1信号通路未被活化,肺组织中mTORC1信号通路下调;进一步发现BCAT1可以与Ras同源基因家族成员C(Ras homolog gene family member C, RhoC)相互作用;此外,BCAT1催化生成的BCKA可以直接结合RhoC,招募Rho鸟嘌呤核苷酸交换因子1(Rho guanine nucleotide exchange factor 1, ARHGEF1),活化RhoC(图1),引起细胞骨架重塑,促进细胞迁移和侵袭^[83]。这些研究凸显了BCAA在细胞内的区室化空间代谢特征,对BCAA及其代谢物的感知有着重要的影响。

2.2 腺苷高半胱氨酸的感知机制

如前所述,细胞内甲硫氨酸丰度的感知可通过SAM-SAMTOR调控mTORC1信号通路。SAM是体内主要的甲基供体,在甲基转移酶作用下,SAM脱去甲基,生成腺苷高半胱氨酸(S-adenosyl-L-homocysteine, SAH)。随后,SAH由腺苷高半胱氨酸水解酶(adenosylhomocysteinase, AHCY)催化水

解成高半胱氨酸和腺苷^[84,85]。研究发现,SAH能通过非mTORC1信号通路在体内外抑制细胞自噬。深入的机制解析阐明了SAH也可以作为信号分子,被类腺苷高半胱氨酸水解酶1(adenosylhomocysteinase like 1, AHCYL1)感知结合,并且二者的结合解离常数(约13 $\mu\text{mol/L}$)位于SAH的生理浓度范围内。值得注意的是,AHCYL1特异性结合SAH而不能结合SAM。在SAH的上下游代谢产物中,AHCYL1也不能结合甲硫氨酸和高半胱氨酸,而仅与腺苷有弱的结合。SAH结合AHCYL1,引起后者变构,使其结合在磷脂酰肌醇3激酶3型催化亚基(phosphatidylinositol 3-kinase catalytic subunit type 3, PIK3C3)的底物结合区,PIK3C3的酶活催化功能受到抑制,其催化产物PtdIns3P水平降低,在细胞和斑马鱼中造成细胞自噬抑制(图1)^[86]。该发现为细胞内甲硫氨酸丰度的感知提供了更深入的视角,反映了其感知机制的多样性。

2.3 精氨酸的非经典感知机制

除了CASTOR和SLC38A9外,目前已发现多个精氨酸感受分子不通过mTORC1通路调控下游信号。

研究人员利用合成光活化精氨酸技术筛选并验证到Bcl2相关抗凋亡基因2(Bcl2-associated athanogene 2, BAG2)为精氨酸结合蛋白(图1)。在精氨酸丰富的条件下,BAG2可与不育ALPHA基序结构域蛋白4B(sterile alpha motif domain containing 4B, SAMD4B)直接结合。精氨酸饥饿时(细胞培养环境中精氨酸浓度为20 $\mu\text{mol/L}$),BAG2与SAMD4B解离,但SAMD4B与 β -连环蛋白(β -catenin)的结合增强。有趣的是,BAG2与 β -catenin结合在SAMD4B的同一个区域,提示BAG2与 β -catenin在精氨酸丰度调控下竞争性结合SAMD4B。在精氨酸饥饿条件下,SAMD4B与 β -catenin结合的同时,也与 β -catenin降解复合物中的其他成分,如糖原合成酶激酶3 β (glycogen synthase kinase-3 β , GSK3 β)结合,介导对 β -catenin的泛素化,最终导致 β -catenin的降解。该研究显示,在精氨酸丰富条件下,BAG2抑制SAMD4B与 β -catenin结合,维持Wnt/ β -catenin稳定,促进肿瘤细胞增殖。而在精氨酸饥饿条件下,BAG2释放的SAMD4B抑制Wnt/ β -catenin信号通路,维持肿瘤细胞的存活^[87]。氨基酸缺乏可以通过GCN2-ATF4激活整合应激反应,值得注意的

是,在精氨酸饥饿条件下,SAMD4B也通过抑制 β -catenin,维持ATF4的蛋白水平,激活整合应激反应,阻止肿瘤细胞死亡^[87]。

另有研究利用精氨酸结合的琼脂糖珠筛选潜在的精氨酸结合蛋白,鉴定到转录调控因子RNA结合基序蛋白39(RNA-binding motif protein 39, RBM39)是新的精氨酸结合蛋白(图1)^[88]。高浓度精氨酸对肝癌生长非常重要,在肝癌细胞中,精氨酸代谢通路受到抑制,但精氨酸直接结合RBM39(细胞培养环境中精氨酸浓度为400 $\mu\text{mol/L}$),促进其入核,RBM39在核内可调控mRNA前体剪切和基因转录^[89]。RBM39感知精氨酸调控代谢相关基因的转录,包括上调天冬酰胺合成酶(asparagine synthetase, ASNS)和磷酸丝氨酸转氨酶1(phosphoserine aminotransferase 1, PSAT1)等基因转录,引起代谢重塑。如ASNS表达的增加上调天冬酰胺的合成,加速精氨酸和天冬氨酸的反向运输,为肝癌细胞摄入更多精氨酸,重塑肿瘤代谢,促进肝癌生长^[89]。值得注意的是,RBM39和ASNS在胚胎肝组织中也高表达。这些结果提示精氨酸感知存在多种机制,细胞通过这些机制在生理或病理条件下适应内外代谢应激环境。

3 展望

从时间、空间上准确定量氨基酸水平及代谢物流向将进一步加深我们对氨基酸感知在各类生理和病理过程中关键作用的理解。代谢物在细胞和亚细胞结构中的生成和分布处于一种动态过程中。在单细胞和亚细胞水平上,实时、定量和定位检测代谢物目前常用的手段之一是利用差速离心结合免疫沉淀技术分离不同组织细胞抽提液的各类细胞器等,通过不同细胞器/亚细胞组分标志物鉴定分离纯度,随后进行质谱分析。但由于细胞内代谢是一个高度动态过程,分离过程中干扰因素引起的批次效应和质谱分析的灵敏度和覆盖度等均会影响结果。值得注意的是,有研究在细胞培养和亚细胞成分分离中采用稳定同位素标记的必需营养物(stable isotope labeling of essential nutrients in cell culture-subcellular fractionation, SILEC-SF),通过该方法引入同位素标记的内标对亚细胞组分中的代谢物进行定量^[90]。此外,不断发展的质谱成像空间代谢组学可以对代谢物空间原位分布进行定量研

究^[91]。对代谢物进行原位研究的另一重要技术方法是开发高性能分子影像探针。其中,配体结合的荧光分子探针是通过受体进行改造,利用配体/底物与受体的特异性结合,使受体发生构象变化,受到激发发出荧光。利用该方法已构建了乳酸、丙酮酸等多种代谢物的荧光探针^[92]。这种分子影像方法与同位素标记相比,更安全,可适用范围广,并且荧光信号更强、更稳定,可在体内外进行实时、定量、可视化监测。开发各类氨基酸及其代谢中间产物的分子影像探针能够为氨基酸代谢及感知研究提供强有力的工具。

深入探究氨基酸感知机制将为健康干预和疾病诊疗提供更精准的策略,如开发靶向氨基酸感知受体的小分子抑制剂^[93]。亮氨酸感知受体LARS1的抑制剂BC-LI-0186可以抑制肿瘤细胞生长,特别是能有效抑制对雷帕霉素耐药的肿瘤细胞的生长^[36]。RBM39感知精氨酸促进肝癌的发展^[88],使用RBM39降解剂Indisulam或者联合氧化剂溴化钾能有效抑制肝癌细胞的生长^[88,89]。很多肿瘤细胞为精氨酸营养缺陷型细胞,必须依赖外源补充的精氨酸,维持细胞内需求。利用精氨酸酶在细胞外降解精氨酸,可造成严重的精氨酸缺乏。目前,这种精氨酸饥饿疗法已在肿瘤患者中开展临床试验,取得了积极的结果^[94,95]。但精氨酸饥饿条件下通过促进SAMD4B抑制 β -catenin和稳定ATF4有可能会成为耐药机制之一^[88]。因此,该精氨酸感知通路的解析,有望为精氨酸饥饿疗法补充新的治疗策略。

以上关于氨基酸感知机制的研究,无论是不同氨基酸通过不同时相调控mTORC1信号通路,还是新的氨基酸代谢中间产物的感知机制及在亚细胞空间定位和不同组织间的感知异同,以及细胞对不同量的氨基酸感知的精细调控,都揭示了细胞内存在氨基酸感知在时、空、量等多维层面的调控网络,这不仅为组织细胞的可塑性和异质性提供了代谢物感知的机制基础,也为氨基酸感知失衡造成的病理效应提供了潜在的精准代谢感知靶向策略。

参考文献

- [1] Wang YP, Li JT, Qu J, et al. Metabolite sensing and signaling in cancer. *J Biol Chem*, 2020, 295: 11938–46.
- [2] Baker SA, Rutter J. Metabolites as signalling molecules.

- Nat Rev Mol Cell Biol, 2023, 24: 355–74.
- [3] Sung Y, Yu YC, Han JM. Nutrient sensors and their crosstalk. *Exp Mol Med*, 2023, 55: 1076–89.
 - [4] Ming H, Tan J, Cao SY, et al. NUFIP1 integrates amino acid sensing and DNA damage response to maintain the intestinal homeostasis. *Nat Metab*, 2025, 7: 120–36.
 - [5] Lin Z, Chang C, Zhao S, et al. Amino acids shape the metabolic and immunologic landscape in the tumor immune microenvironment: from molecular mechanisms to therapeutic strategies. *Cancer Biol Med*, 2025, 22: 726–46.
 - [6] Yue S, Li G, He S, et al. The central role of mTORC1 in amino acid sensing. *Cancer Res*, 2022, 82: 2964–74.
 - [7] Valenstein ML, Wranik M, Lalgudi PV, et al. Structural basis for the dynamic regulation of mTORC1 by amino acids. *Nature*, 2025, 646: 493–500.
 - [8] Zhang P, McGrath BC, Reinert J, et al. The GCN2 eIF2 α kinase is required for adaptation to amino acid deprivation in mice. *Mol Cell Biol*, 2002, 22: 6681–8.
 - [9] Zhang C, Han Y, Yao W, et al. Mechanisms of mTORC1 and GCN2 amino acid sensing pathways in tumorigenesis and metastatic progression (Review). *Int J Mol Med*, 2026, 57: 13.
 - [10] He L, Cho S, Blenis J. mTORC1, the maestro of cell metabolism and growth. *Genes Dev*, 2025, 39: 109–31.
 - [11] Cui Z, Joiner AMN, Jansen RM, et al. Amino acid sensing and lysosomal signaling complexes. *Curr Opin Struct Biol*, 2023, 79: 102544.
 - [12] Walchli M, Berneiser K, Mangia F, et al. Regulation of human mTOR complexes by DEPTOR. *Elife*, 2021, 10: e70871.
 - [13] Zhang H, Xiao X, Pan Z, et al. mTOR signaling networks: mechanistic insights and translational frontiers in disease therapeutics. *Signal Transduct Target Ther*, 2025, 10: 428.
 - [14] Valenstein ML, Lalgudi PV, Gu X, et al. Rag-Ragulator is the central organizer of the physical architecture of the mTORC1 nutrient-sensing pathway. *Proc Natl Acad Sci U S A*, 2024, 121: e2322755121.
 - [15] Cui Z, Esposito A, Napolitano G, et al. Structural basis for mTORC1 activation on the lysosomal membrane. *Nature*, 2025, 647: 536–43.
 - [16] Groenewoud MJ, Zwartkruis FJ. Rheb and Rags come together at the lysosome to activate mTORC1. *Biochem Soc Trans*, 2013, 41: 951–5.
 - [17] Shen K, Huang RK, Brignole EJ, et al. Architecture of the human GATOR1 and GATOR1-Rag GTPases complexes. *Nature*, 2018, 556: 64–9.
 - [18] Egri SB, Ouch C, Chou HT, et al. Cryo-EM structures of the human GATOR1-Rag-Ragulator complex reveal a spatial-constraint regulated GAP mechanism. *Mol Cell*, 2022, 82: 1836–49.e5.
 - [19] Sahu U, Ben-Sahra I. GATOR2 rings GATOR1 to speak to mTORC1. *Mol Cell*, 2023, 83: 6–8.
 - [20] Valenstein ML, Rogala KB, Lalgudi PV, et al. Structure of the nutrient-sensing hub GATOR2. *Nature*, 2022, 607: 610–6.
 - [21] Wolfson RL, Chantranupong L, Wyant GA, et al. KICSTOR recruits GATOR1 to the lysosome and is necessary for nutrients to regulate mTORC1. *Nature*, 2017, 543: 438–42.
 - [22] Lupton CJ, Bayly-Jones C, Dong S, et al. Structure of the lysosomal KICSTOR-GATOR1-SAMTOR nutrient-sensing supercomplex. *Cell*, 2026, 189: 1185–200.e28.
 - [23] Meng D, Yang Q, Wang H, et al. Glutamine and asparagine activate mTORC1 independently of Rag GTPases. *J Biol Chem*, 2020, 295: 2890–9.
 - [24] Fernandes SA, Angelidaki DD, Nuchel J, et al. Spatial and functional separation of mTORC1 signalling in response to different amino acid sources. *Nat Cell Biol*, 2024, 26: 1918–33.
 - [25] Wolfson RL, Chantranupong L, Saxton RA, et al. Sestrin2 is a leucine sensor for the mTORC1 pathway. *Science*, 2016, 351: 43–8.
 - [26] Chen J, Ou Y, Luo R, et al. SAR1B senses leucine levels to regulate mTORC1 signalling. *Nature*, 2021, 596: 281–4.
 - [27] Han JM, Jeong SJ, Park MC, et al. Leucyl-tRNA synthetase is an intracellular leucine sensor for the mTORC1-signaling pathway. *Cell*, 2012, 149: 410–24.
 - [28] Saxton RA, Knockenhauer KE, Wolfson RL, et al. Structural basis for leucine sensing by the Sestrin2-mTORC1 pathway. *Science*, 2016, 351: 53–8.
 - [29] Chantranupong L, Wolfson RL, Orozco JM, et al. The Sestrins interact with GATOR2 to negatively regulate the amino-acid-sensing pathway upstream of mTORC1. *Cell Rep*, 2014, 9: 1–8.
 - [30] Su MY, Teng F, Wang S, et al. Cryo-EM structures of amino acid sensors bound to the human GATOR2 complex. *Cell Rep*, 2025, 44: 116088.
 - [31] Kim S, Yoon I, Son J, et al. Leucine-sensing mechanism of leucyl-tRNA synthetase 1 for mTORC1 activation. *Cell Rep*, 2021, 35: 109031.
 - [32] Kim K, Yoo HC, Kim BG, et al. O-GlcNAc modification of leucyl-tRNA synthetase 1 integrates leucine and glucose availability to regulate mTORC1 and the metabolic fate of leucine. *Nat Commun*, 2022, 13: 2904.
 - [33] Yoon MS, Son K, Arauz E, et al. Leucyl-tRNA

- synthetase activates Vps34 in amino acid-sensing mTORC1 signaling. *Cell Rep*, 2016, 16: 1510–7.
- [34] Takahara T, Amemiya Y, Sugiyama R, et al. Amino acid-dependent control of mTORC1 signaling: a variety of regulatory modes. *J Biomed Sci*, 2020, 27: 87.
- [35] Wauson EM, Lorente-Rodriguez A, Cobb MH. Minireview: nutrient sensing by G protein-coupled receptors. *Mol Endocrinol*, 2013, 27: 1188–97.
- [36] Kim JH, Lee C, Lee M, et al. Control of leucine-dependent mTORC1 pathway through chemical intervention of leucyl-tRNA synthetase and RagD interaction. *Nat Commun*, 2017, 8: 732.
- [37] Son SM, Park SJ, Lee H, et al. Leucine signals to mTORC1 via its metabolite acetyl-coenzyme A. *Cell Metab*, 2019, 29: 192–201.e7.
- [38] Li JT, Yang H, Lei MZ, et al. Dietary folate drives methionine metabolism to promote cancer development by stabilizing MAT IIA. *Signal Transduct Target Ther*, 2022, 7: 192.
- [39] Li ML, Cao SY, Qu J, et al. S-adenosyl-L-methionine supplementation alleviates damaged intestinal epithelium and inflammatory infiltration caused by Mat2a deficiency. *Development*, 2023, 150: dev201135.
- [40] Tang X, Zhang Y, Wang G, et al. Molecular mechanism of S-adenosylmethionine sensing by SAMTOR in mTORC1 signaling. *Sci Adv*, 2022, 8: eabn3868.
- [41] Gu X, Orozco JM, Saxton RA, et al. SAMTOR is an S-adenosylmethionine sensor for the mTORC1 pathway. *Science*, 2017, 358: 813–8.
- [42] Jiang C, Liu J, He S, et al. PRMT1 orchestrates with SAMTOR to govern mTORC1 methionine sensing via Arg-methylation of NPRL2. *Cell Metab*, 2023, 35: 2183–99.e7.
- [43] Liu GY, Jouandin P, Bahng RE, et al. An evolutionary mechanism to assimilate new nutrient sensors into the mTORC1 pathway. *Nat Commun*, 2024, 15: 2517.
- [44] Zhou Y, Ren J, Song T, et al. Methionine regulates mTORC1 via the T1R1/T1R3-PLC β -Ca²⁺-ERK1/2 signal transduction process in C2C12 cells. *Int J Mol Sci*, 2016, 17: 1684.
- [45] Zhou Y, Zhou Z, Peng J, et al. Methionine and valine activate the mammalian target of rapamycin complex 1 pathway through heterodimeric amino acid taste receptor (TAS1R1/TAS1R3) and intracellular Ca²⁺ in bovine mammary epithelial cells. *J Dairy Sci*, 2018, 101: 11354–63.
- [46] Morris SM Jr. Arginine metabolism revisited. *J Nutr*, 2016, 146: 2579S–86S.
- [47] Albaugh VL, Pinzon-Guzman C, Barbul A. Arginine—Dual roles as an onconutrient and immunonutrient. *J Surg Oncol*, 2017, 115: 273–80.
- [48] Chantranupong L, Scaria SM, Saxton RA, et al. The CASTOR proteins are arginine sensors for the mTORC1 pathway. *Cell*, 2016, 165: 153–64.
- [49] Jansen RM, Maghe C, Tapia K, et al. Structural basis for mTORC1 regulation by the CASTOR1-GATOR2 complex. *Nat Struct Mol Biol*, 2025, 32: 1980–8.
- [50] Saxton RA, Chantranupong L, Knockenhauer KE, et al. Mechanism of arginine sensing by CASTOR1 upstream of mTORC1. *Nature*, 2016, 536: 229–33.
- [51] Liu C, Zhang Y, Wang Y, et al. CASTOR1 and CASTOR2 respond to different arginine levels to regulate mTORC1 activity. *Mol Cell*, 2026, 86: 362–75 e4.
- [52] Wang S, Tsun ZY, Wolfson RL, et al. Metabolism. Lysosomal amino acid transporter SLC38A9 signals arginine sufficiency to mTORC1. *Science*, 2015, 347: 188–94.
- [53] Wyant GA, Abu-Remaileh M, Wolfson RL, et al. mTORC1 activator SLC38A9 is required to efflux essential amino acids from lysosomes and use protein as a nutrient. *Cell*, 2017, 171: 642–54.e12.
- [54] Lei HT, Mu X, Hattne J, et al. A conformational change in the N terminus of SLC38A9 signals mTORC1 activation. *Structure*, 2021, 29: 426–32.e8.
- [55] Jung JW, Macalino SJY, Cui M, et al. Transmembrane 4 L six family member 5 senses arginine for mTORC1 signaling. *Cell Metab*, 2019, 29: 1306–19.e7.
- [56] Carroll B, Maetzel D, Maddocks OD, et al. Control of TSC2-Rheb signaling axis by arginine regulates mTORC1 activity. *Elife*, 2016, 5: e11058.
- [57] Yang H, Yu Z, Chen X, et al. Structural insights into TSC complex assembly and GAP activity on Rheb. *Nat Commun*, 2021, 12: 339.
- [58] Bernfeld E, Menon D, Vaghela V, et al. Phospholipase D-dependent mTOR complex 1 (mTORC1) activation by glutamine. *J Biol Chem*, 2018, 293: 16390–401.
- [59] Meng D, Yang Q, Jeong MH, et al. SNAT7 regulates mTORC1 via macropinocytosis. *Proc Natl Acad Sci U S A*, 2022, 119: e2123261119.
- [60] Hatakeyama R. Pib2 as an emerging master regulator of yeast TORC1. *Biomolecules*, 2021, 11: 1489.
- [61] Tanigawa M, Yamamoto K, Nagatoishi S, et al. A glutamine sensor that directly activates TORC1. *Commun Biol*, 2021, 4: 1093.
- [62] Zeng Q, Araki Y, Noda T. Pib2 is a cysteine sensor involved in TORC1 activation in *Saccharomyces cerevisiae*. *Cell Rep*, 2024, 43: 113599.

- [63] Duran RV, Oppliger W, Robitaille AM, et al. Glutaminolysis activates Rag-mTORC1 signaling. *Mol Cell*, 2012, 47: 349–58.
- [64] Bodineau C, Tome M, Courtois S, et al. Two parallel pathways connect glutamine metabolism and mTORC1 activity to regulate glutamoptosis. *Nat Commun*, 2021, 12: 4814.
- [65] Berquez M, Chen Z, Festa BP, et al. Lysosomal cystine export regulates mTORC1 signaling to guide kidney epithelial cell fate specialization. *Nat Commun*, 2023, 14: 3994.
- [66] Masson GR. Towards a model of GCN2 activation. *Biochem Soc Trans*, 2019, 47: 1481–8.
- [67] Altintas O, MacArthur MR. General control nonderepressible 2 (GCN2) as a therapeutic target in age-related diseases. *Front Aging*, 2024, 5: 1447370.
- [68] Zhou C, Zhang M, Murray J, et al. GCN1 couples GCN2 to ribosomal state to initiate amino acid response pathway signaling. *Science*, 2025, 390: eads8728.
- [69] Humeau J, Leduc M, Cerrato G, et al. Phosphorylation of eukaryotic initiation factor-2alpha (eIF2alpha) in autophagy. *Cell Death Dis*, 2020, 11: 433.
- [70] Hu X, Guo F. Amino acid sensing in metabolic homeostasis and health. *Endocr Rev*, 2021, 42: 56–76.
- [71] Ge MK, Zhang C, Zhang N, et al. The tRNA-GCN2-FBXO22-axis-mediated mTOR ubiquitination senses amino acid insufficiency. *Cell Metab*, 2023, 35: 2216–30.e8.
- [72] Figlia G, Muller S, Garcia-Cortizo F, et al. mTORC1 senses glutamine and other amino acids through GCN2. *EMBO J*, 2025, 44: 4825–66.
- [73] Corradetti MN, Inoki K, Guan KL. The stress-induced proteins RTP801 and RTP801L are negative regulators of the mammalian target of rapamycin pathway. *J Biol Chem*, 2005, 280: 9769–72.
- [74] Doglioni G, Fernandez-Garcia J, Igelmann S, et al. Aspartate signalling drives lung metastasis via alternative translation. *Nature*, 2025, 638: 244–50.
- [75] Willard SS, Koochekpour S. Glutamate, glutamate receptors, and downstream signaling pathways. *Int J Biol Sci*, 2013, 9: 948–59.
- [76] Felig P, Marliss E, Cahill GF Jr. Plasma amino acid levels and insulin secretion in obesity. *N Engl J Med*, 1969, 281: 811–6.
- [77] Cirulli ET, Guo L, Leon Swisher C, et al. Profound perturbation of the metabolome in obesity is associated with health risk. *Cell Metab*, 2019, 29: 488–500.e2.
- [78] Ma QX, Zhu WY, Lu XC, et al. BCAA-BCKA axis regulates WAT browning through acetylation of PRDM16. *Nat Metab*, 2022, 4: 106–22.
- [79] Newgard CB, An J, Bain JR, et al. A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. *Cell Metab*, 2009, 9: 311–26.
- [80] Patrick M, Gu Z, Zhang G, et al. Metabolon formation regulates branched-chain amino acid oxidation and homeostasis. *Nat Metab*, 2022, 4: 1775–91.
- [81] Yin M, Lei QY. BCAT2-BCKDH metabolon maintains BCAA homeostasis. *Nat Metab*, 2022, 4: 1618–9.
- [82] Alotaibi AZ, AlMalki RH, Sebaa R, et al. Insights from metabolomics profiling of MSUD in pediatrics toward disease progression. *Metabolites*, 2025, 15: 658.
- [83] Qian L, Li N, Lu XC, et al. Enhanced BCAT1 activity and BCAA metabolism promotes RhoC activity in cancer progression. *Nat Metab*, 2023, 5: 1159–73.
- [84] Bravo AC, Aguilera MNL, Marziali NR, et al. Analysis of S-adenosylmethionine and S-adenosylhomocysteine: method optimisation and profiling in healthy adults upon short-term dietary intervention. *Metabolites*, 2022, 12: 373.
- [85] Cueto R, Shen W, Liu L, et al. SAH is a major metabolic sensor mediating worsening metabolic crosstalk in metabolic syndrome. *Redox Biol*, 2024, 73: 103139.
- [86] Huang W, Li N, Zhang Y, et al. AHCYL1 senses SAH to inhibit autophagy through interaction with PIK3C3 in an mTORC1-independent manner. *Autophagy*, 2022, 18: 309–19.
- [87] Chen MY, Sun CY, Zhao R, et al. BAG2 releases SAMD4B upon sensing of arginine deficiency to promote tumor cell survival. *Mol Cell*, 2025, 85: 2581–96.e6.
- [88] Mossmann D, Muller C, Park S, et al. Arginine reprograms metabolism in liver cancer via RBM39. *Cell*, 2023, 186: 5068–83.e23.
- [89] An H, Xia A, Liu S, et al. RBM39 promotes base excision repair to facilitate the progression of HCC by stabilising OGG1 mRNA. *Cell Prolif*, 2025, 58: e70059.
- [90] Trefely S, Huber K, Liu J, et al. Quantitative subcellular acyl-CoA analysis reveals distinct nuclear metabolism and isoleucine-dependent histone propionylation. *Mol Cell*, 2022, 82: 447–62.e6.
- [91] Wang G, van den Berg BM, Kostidis S, et al. Spatial quantitative metabolomics enables identification of remote and sustained ipsilateral cortical metabolic reprogramming after stroke. *Nat Metab*, 2025, 7: 1791–800.
- [92] Gest AMM, Sahan AZ, Zhong Y, et al. Molecular spies in action: genetically encoded fluorescent biosensors

- light up cellular signals. *Chem Rev*, 2024, 124: 12573–660.
- [93] Mannick JB, Lamming DW. Targeting the biology of aging with mTOR inhibitors. *Nat Aging*, 2023, 3: 642–60.
- [94] Chu YD, Lai MW, Yeh CT. Unlocking the potential of arginine deprivation therapy: recent breakthroughs and promising future for cancer treatment. *Int J Mol Sci*, 2023, 24: 10668.
- [95] Szlosarek PW, Creelan BC, Sarkodie T, et al. Pegargi-minase plus first-line chemotherapy in patients with nonepithelioid pleural mesothelioma: the ATOMIC-Meso Randomized Clinical Trial. *JAMA Oncol*, 2024, 10: 475–83.