Advances in Amino Acid Transport and Sensing Systems in Animals (Postprint)

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Abstract

Amino acid transporters exhibit both transport activity and can function as sensors to mediate extracellular amino acid sensing. Transporters located on the cell membrane, particularly those that transport large neutral amino acids including leucine, are capable of regulating cellular metabolism via intracellular nutrient signaling pathways, such as the mammalian target of rapamycin complex 1 (mTORC1) pathway that controls cell growth and the general control nonderepressible kinase (GCN) pathway that is activated upon amino acid starvation. In view of the significance of amino acid transporter research for animal nutrition, this review summarizes the classification of amino acid transporters, their mediated amino acid sensing functions, and their tissue specificity, with the aim of advancing related research endeavors.

Full Text

Advances in Amino Acid Transport and Sensing Systems in Animals

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Abstract: Amino acid transporters function not only as carriers but also as receptors that sense extracellular amino acid levels. Membrane-bound amino acid transporters, particularly those transporting large neutral amino acids such as leucine, regulate cellular metabolism through intracellular nutrient signaling pathways, including the mammalian target of rapamycin complex 1 (mTORC1) pathway that controls cell growth and the general control nonderepressible kinase (GCN) pathway activated by amino acid starvation. Given the importance

of amino acid transporter research to animal nutrition, this review summarizes the classification of amino acid transporters, their amino acid sensing functions, and tissue-specific expression patterns to support future research in this field.

Keywords: amino acid transport; amino acid sensing; mTORC1 pathway; GCN pathway

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Amino acids are among the most important substances constituting animal organisms, influencing growth and development in various ways. The twenty L-amino acids provide substrates for protein synthesis, and under special conditions, amino acids can also generate energy equivalent to carbohydrates for most cellular metabolic processes. Furthermore, amino acids supply intermediates for the tricarboxylic acid cycle and gluconeogenesis, serve as precursors for hormones and neurotransmitters, and play crucial roles in specialized metabolic processes such as polyamine, creatine, and phosphatidylserine metabolism. Consequently, organisms require efficient regulatory mechanisms to balance intracellular and extracellular amino acid concentrations to maintain homeostasis, a process in which amino acid transporters play a vital role.

Christensen pioneered research on amino acid transporters in mammalian cells, discovering competitive relationships among several amino acids during cellular uptake and subsequently demonstrating the existence of amino acid transporters through molecular cloning. While the mTORC1 and GCN pathways related to amino acid metabolism have been extensively studied, research on amino acid transport mechanisms and signal sensing remains limited. This review summarizes recent advances in these areas to provide a foundation for future investigations.

1. Classification of Amino Acid Transporters

The phospholipid bilayer of cell membranes acts as a selective barrier that prevents large molecules such as amino acids from diffusing across, necessitating transmembrane carriers for their transport. Amino acid transporters selectively couple with counter-transport of Na , H , K , and Cl . Modern classification of mammalian amino acid transporters is based on gene sequence similarity, gradually replacing traditional classification by "systems" (functional characteristics, substrate specificity, ion dependence, pH sensitivity, and kinetic properties).

The binding sites of mammalian amino acid transporters typically recognize a series of structurally similar amino acids, which can be categorized as large neutral amino acids (LNAAs), small neutral amino acids (SNAAs), cationic amino acids (CAAs), and anionic amino acids (AAAs). Six major amino acid transporter superfamilies have been identified: solute carrier family (SLC) members 1 (SLC1), SLC6, SLC7, SLC36, SLC38, and SLC43. Additionally, SLC16 functions as a monocarboxylate transporter capable of transporting aromatic amino acids. These transporters typically feature 10–12 transmembrane domains sur-

rounding a central pore region. Although the SLC3 family is also classified as amino acid transporters, their structure is atypical, consisting of single transmembrane domain glycoproteins that function as regulatory subunits for the SLC7 family.

The SLC1 family comprises five high-affinity glutamine (Gln) transporters (SLC1A1, SLC1A2, SLC1A3, SLC1A6, SLC1A7) and two neutral amino acid transporters (SLC1A4 and SLC1A5). SLC1A5 encodes the alanine (Ala)-serine (Ser)-cysteine (Cys) transporter 2 (ASCT2), which preferentially transports Gln despite its name. ASCT2 is a selective bidirectional transporter that mediates the exchange of Gln, Ser, asparagine (Asn), and threonine (Thr), while Ala, valine (Val), and methionine (Met) can only be transported from the extracellular to intracellular space.

The SLC7 family represents an important Gln transporter family with 13 members divided into two subgroups: cationic amino acid transporters (CATs) and L-amino acid transporters (LATs). The 4F2 cell-surface antigen heavy chain (4F2hc) is a multifunctional protein involved in immune system regulation, cell activation, growth, and adhesion. It forms the LAT1/4F2hc heterodimer with proteins encoded by SLC3A2 and SLC7A5 genes to transport essential amino acids. LAT2 can also co-express with 4F2hc to transport amino acids, but with distinct substrate preferences: the LAT1/4F2hc complex preferentially transports LNAAs such as leucine (Leu), whereas the LAT2/4F2hc complex has a broader substrate range that includes small amino acids such as Ala and glycine (Gly). Additionally, the LAT1/4F2hc complex exhibits low affinity for Gln, while the LAT2/4F2hc complex shows high affinity.

The SLC38 family belongs to the amino acid polyamine-organic cation (APC) family, which includes 11 members that mediate transport of neutral amino acids such as Gln and Ala, as well as histidine (His), arginine (Arg), and aspartate (Asp). Well-characterized members include SLC38A1, SLC38A2, SLC38A3, SLC38A4, and SLC38A5.

The reported SLC superfamilies and their systematic classifications are summarized in Table 1.

Table 1 SLC Superfamily and System Classification

System	Amino Acid Substrates	Protein Name	Gene Name
Neutral Amino Acid Transporters			
A	Ala, Gly, Leu, Ile, Met, Gln, His, Val	SNAT1	SLC38A1

System	Amino Acid Substrates	Protein Name	Gene Name
A	Ala, Gly, Leu, Ile, Met, Gln, His, Val	SNAT2	SLC38A2
A	Ala, Gly, Leu, Ile, Met, Gln, His, Val	SNAT4	SLC38A4
ASC	Ala, Ser, Cys, Gly, Leu, Ile, Val, Thr, Gln	ASCT1	SLC1A4
ASC	Ala, Ser, Cys, Gly, Leu, Ile, Val, Thr, Gln	ASCT2	SLC1A5
B ,	Leu, Cys, Val, Ile, Phe, Met, Ser, Ala, Gln, Arg, Asn, His	ATB ,	SLC6A14
B	Leu, Phe, Met, His, Ile, Val	B AT1	SLC6A19
B	Leu, Phe, Met, His, Ile, Val	B AT2	SLC6A15
N	Arg, Gln, Asn, His	SNAT3	SLC38A3
N	Arg, Gln, Asn, His	SNAT5	SLC38A5
L	Leu, Phe, Met, His, Ile, Val	LAT1	SLC7A5
L	Leu, Phe, Met, His, Ile, Val	LAT2	SLC7A8
y L	Arg, Gln, Asn, His	y LAT1	SLC7A6
y L	Arg, Gln, Asn, His	y LAT2	SLC7A7
LAT3	Leu, Phe, Met, His, Ile, Val	LAT3	SLC43A1
LAT4	Leu, Phe, Met, His, Ile, Val	LAT4	SLC43A2
Cationic Amino Acid Trans-porters			
y	Arg, Lys	CAT-1	SLC7A1
y	Arg, Lys	CAT-2	SLC7A2
y	Arg, Lys	CAT-3	SLC7A3
Anionic Amino Acid Trans-porters			
X AG	Glu, Asp	EAAT3	SLC1A1
X AG	Glu, Asp	EAAT2	SLC1A2
X AG	Glu, Asp	EAAT1	SLC1A3

Note: Ala, alanine; Gly, glycine; Leu, leucine; Ile, isoleucine; Met, methionine; Gln, glutamine; His, histidine; Val, valine; Ser, serine; Cys, cysteine; Thr, threonine; Phe, phenylalanine; Arg, arginine; Asn, asparagine; Trp, tryptophan; Lys, lysine; Glu, glutamic acid; Asp, aspartate; SNAT, sodium-coupled neutral amino acid transporter; ASCT, alanine-serine-cysteine transporter; ATB , , sodium- and chloride-dependent neutral and basic amino acid transporter; B AT,

sodium-dependent neutral amino acid transporter; LAT, L-type amino acid transporter; CAT, cationic amino acid transporter; EAAT, excitatory amino acid transporter; SLC, solute carrier family member.

2. Amino Acid Sensing Signaling Pathways Mediated by Amino Acid Transporters

Two primary amino acid sensing signaling pathways are mediated by amino acid transporters: the mTORC1 pathway and the GCN pathway. The mTORC1 pathway is activated under high concentrations of specific amino acids and monitors amino acid levels in both the cytoplasm and subcellular compartments such as lysosomes. The GCN pathway primarily senses amino acid concentrations bound to tRNA in the cytoplasm, with GCN2 playing a central role in this process.

2.1 mTORC1 Pathway

mTORC1 comprises three essential components: mammalian target of rapamycin (mTOR), regulatory-associated protein of mTOR (Raptor), and mammalian lethal with SEC13 protein 8 (mLST8, also known as G L). mTOR, the central component of the mTORC1 complex, is a Ser-Thr kinase that plays a pivotal role in regulating cell growth, protein synthesis, and autophagy. Raptor facilitates substrate binding to the target of rapamycin signaling (TOS) motif to form the mTORC1 complex, while mLST8 is associated with the catalytic activity of the protein and stabilizes the kinase activation loop. In addition to these three essential parts, mTORC1 contains two inhibitory subunits: proline-rich AKT1 substrate 1 (PRAS40) and DEP domain-containing mTOR-interacting protein (DEPTOR).

The mTORC1 signaling pathway can be activated through multiple upstream pathways, including the phosphatidylinositol 3-kinase (PI3K)-protein kinase B (Akt)-mTORC1 pathway and the liver kinase B1 (LKB1)-AMP-activated protein kinase (AMPK)-mTORC1 pathway. Upon activation, mTORC1 regulates protein synthesis by controlling the phosphorylation of downstream ribosomal protein S6 kinase 1 (S6K1) and eukaryotic translation initiation factor 4E binding protein (4EBP). The mTORC1 signaling pathway represents a key anabolic signaling mechanism within cells that responds to nutrient levels, growth factors, energy stress, and hypoxic stimuli.

Essential amino acids, including leucine (Leu), tryptophan (Trp), phenylalanine (Phe), and arginine (Arg), can activate the mTORC1 pathway. The response of mTORC1 to amino acid concentrations is mediated by two GTPases: Rag GTPase and Ras homolog enriched in brain GTPase (Rheb GTPase). Amino acid activation of the mTORC1 pathway requires mediation by lysosomal membrane G-proteins and Rheb GTPase, which positively regulates mTORC1 signaling through downstream tuberous sclerosis complex 2 (TSC2). Recent studies have identified several intracellular amino acid sensors associated with the mTORC1

signaling pathway, including leucyl-tRNA synthetase (LRS), glutamate dehydrogenase (GDH), and branched-chain amino acid receptor 1. LRS is highly sensitive to intracellular Leu concentrations and activates the mTORC1 pathway by translocating to lysosomes and promoting nucleotide binding to Rag GTPase. The vacuolar H -ATPase located on lysosomal membranes is highly sensitive to amino acid accumulation and can directly activate mTORC1 signaling by acting on Rag GTPase, representing a recently discovered important intracellular amino acid sensor.

Kim et al. demonstrated that selective glucagon receptor inhibition increases expression of the neutral amino acid transporter SLC38A5, which regulates pancreatic -cell proliferation in mice through the mTORC1 signaling pathway. Pinilla et al. showed that amino acid substrates of SLC38A2 and essential branched-chain amino acids increase mTORC1-dependent S6K1 phosphorylation levels. Nicklin et al. reported that inhibition of amino acid transporters SLA1A5 and SLC7A5 suppresses mTORC1 pathway activation in HeLa cells by limiting Gln and Leu uptake.

2.2 GCN Pathway

GCN2 belongs to the eukaryotic initiation factor 2 (eIF2) kinase family and senses specific amino acid deficiencies within cells by directly binding to uncharged tRNAs. Phosphorylation of eIF2 disrupts the Met initiation codon, thereby preventing mRNA translation initiation and reducing globin synthesis. Following amino acid starvation, this response facilitates selective translation of mRNAs encoding genes related to protein synthesis, modification, and clearance. In many cell types, a crucial function of the GCN signaling pathway is the upregulation of amino acid transporter SLC38A2 gene expression during amino acid deficiency, a process termed "adaptive regulation" that involves transcriptional activation and increased SLC38A2 mRNA translation and stability (reduced degradation). During GCN signal transduction, amino acid transporters function as both "transporters" and "receptors," and carriers possessing both transport and sensing capabilities are termed "transceptors." Currently identified transceptors include SLC38A2 and SLC36A1, which can sense amino acid abundance independently of their transport function.

3. Tissue Specificity of Amino Acid Transporters and Amino Acid Sensing

Research on amino acid transporters in regulating protein synthesis has increased substantially in recent years. The mechanisms of intracellular amino acid availability sensing, mTORC1 pathway activation, and protein synthesis machinery are gradually being elucidated, while the expression and localization of multiple amino acid transporters and sensors in different tissues and cell types have been investigated and revealed.

3.1 Amino Acid Transport and Sensing in Skeletal Muscle and Mammary Tissue

Studies have shown that expression of amino acid transporters in human skeletal muscle is dynamic and responsive to various stimuli, indicating a unique regulatory role in skeletal muscle adaptation. A better understanding of these mechanisms will help optimize nutritional strategies to improve skeletal muscle health.

Research demonstrates that specific amino acid transporter expression increases in skeletal muscle of elderly individuals following resistance training and amino acid infusion. In healthy young adults, amino acid infusion significantly increases mRNA expression of amino acid transporters SLC7A5, SLC38A2, and SLC36A1 in skeletal muscle cells. Following amino acid infusion into skeletal muscle, increased protein expression can persist for 2–3 hours even as amino acid levels gradually return to normal. In both animal and human skeletal muscle, intracellular amino acid availability primarily regulates protein synthesis through the mTORC1 signaling pathway, whose activation promotes skeletal muscle protein synthesis and reduces autophagy. Recent studies indicate that amino acid transporters have integrated effects on both intracellular and extracellular amino acid concentration changes in skeletal muscle, playing a central role in amino acid transport while also sensing extracellular amino acid status through transceptors. Muscle-specific knockout of SLC7A5 in mice fed high-protein diets results in mild insulin resistance accompanied by mTORC1 pathway activation.

In 1985, Baumrucker initially elucidated the functional characteristics of amino acids in bovine mammary tissue. Essential amino acids, particularly leucine, play important regulatory roles in milk protein synthesis. Leu primarily enters cells through L transport systems, such as LAT1 (SLC7A5) coupled with CD98 (SLC3A2), LAT3 (SLC7A7), and the y system LAT3 (SLC43A1), with LAT1 commonly used to study amino acid-dependent mTORC1 pathway activation. Transport of Gln into cells by ASCT2 (SLC1A5), SNAT2 (SLC38A2), and SNAT4 (SLC38A4) is a prerequisite for Leu transmembrane transport. Moshel et al. found that removal of all amino acids or selective removal of Leu from culture medium of bovine mammary epithelial cells reduces mTORC1-mediated expression of milk proteins and -lactoglobulin. Increased amino acid supply stimulates GDP-to-GTP conversion, localizing GTP to Rag heterodimers, which then bind to mTORC1 and translocate to lysosomal membranes for further action. Leu supply affects casein synthesis in mammary epithelial cells, and supplementation with multiple amino acids including Leu promotes phosphorylation of mTORC1 pathway-related proteins.

Specific amino acid transporters not only transport amino acids across membranes but also influence protein synthesis through the mTORC1 signaling pathway. Drummond et al. reported that increased essential amino acids upregulate gene expression of LAT1, CD98, and the Na -coupled neutral amino acid transporter SLC38A2, enhancing protein anabolism through the mTORC1

pathway. Inhibition of specific amino acid transporter activity while increasing amino acid concentrations fails to activate and instead suppresses the mTORC1 signaling pathway. Li et al. demonstrated that optimal ratios of essential amino acids stimulate -casein synthesis in mammary epithelial cells via the mTORC1 pathway. Gao et al. found that individual supplementation with different concentrations of Leu or His regulates milk protein synthesis through the mTORC1 pathway.

Beyond mammary epithelial cells, amino acid transporters in other tissue epithelial cells can also activate the mTORC1 signaling pathway. Na -coupled neutral amino acid transporter SLC6A19 knockout mice exhibit obvious amino acid starvation symptoms in intestinal and renal epithelial cells. The Na /Cl -coupled amino acid transporter SLC6A14, which uses neutral amino acids and CAAs as substrates, is significantly upregulated during the mammalian blastocyst stage, providing sufficient amino acids—particularly Leu—for blastocyst activation and trophoblast growth. Placental growth is regulated by the mTORC1 signaling pathway, which can affect post-translational modification or translocation of amino acid transporters on the placental surface.

4. Conclusions

Amino acid transporters play crucial roles in mammalian cell growth and metabolism, regulating nutritional balance through both mTORC1 and GCN signaling pathways. In vitro cell experiments have provided the molecular basis for understanding amino acid sensing, but researchers typically study mTORC1 pathway activation by adding 2–5 times the physiological concentration of amino acid mixtures to culture medium or by adding amino acids after amino acid starvation treatment. These approaches deviate somewhat from actual metabolic conditions in animal organisms and require further investigation and refinement by future researchers.

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