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FOCUSED REVIEW

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The human LAT1–4F2hc (SLC7A5–SLC3A2) transporter complex: Physiological and pathophysiological implications

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Abstract

LAT1 and 4F2hc form a heterodimeric membrane protein complex, which functions as one of the best characterized amino acid transporters. Since LAT1–4F2hc is required for the efficient uptake of essential amino acids and hormones, it promotes cellular growth, in part, by stimulating mTORC1 (mechanistic target of rapamycin complex 1) signalling and by repressing the integrated stress response (ISR). Gain or loss of LAT1–4F2hc function is associated with cancer, diabetes, and immunological and neurological diseases. Hence, LAT1–4F2hc represents an attractive drug target for disease treatment. Specific targeting of LAT1–4F2hc will be facilitated by the increasingly detailed understanding of its molecular architecture, which provides important concepts for its function and regulation. Here, we summarize (i) structural insights that help to explain how LAT1 and 4F2hc assemble to transport amino acids across membranes, (ii) the role of LAT1–4F2hc in key metabolic signalling pathways, and (iii) how derailing these processes could contribute to diseases.

KEYWORDS
4F2hc, disease, integrated stress response, LAT1, mTORC1

1 | INTRODUCTION

Cells use amino acids as building blocks for protein synthesis or as fuels for metabolic reactions. Inside cells, amino acids are sensed by signal transduction pathways that regulate and coordinate cellular metabolism with growth. In addition to these intracellular roles, amino acids can function as intercellular signalling molecules when they are exchanged between cells. The cellular release and the uptake of amino acids is mediated by amino acid transporters. Amino acid transporters are transmembrane proteins that facilitate the transfer of amino acids between different organs, cells and intracellular compartments. Thereby, they determine the quantity and quality of amino acids pools on the organismal, cellular, and subcellular level. To execute this task, the human genome encodes at least 66 amino acid transporters, which belong to 11 individual solute carrier (SLC) families (reviewed in Kandasamy et al.[1]). The function of most amino acid transporters is undercharacterized. Notable exceptions are the members of the SLC7 family, which are well studied and have important physiological and pathophysiological roles.

2 | THE SLC7 FAMILY

The SLC7 family has 13 members, which can be grouped into the cationic amino acid transporters (CATs, members SLC7A1–SLC7A4, and SLC7A14), and the L-type

amino acid transporters (LATs, SLC7A5–11, and SLC7A13). These amino acid transporters differ with respect to substrate transport (reviewed in previous works[1–3]). CATs function as monomers and are *N*-glycosylated. LATs are also called nonglycosylated light chain transporters, and they interact with glycosylated heavy chain transporters from the SLC3 family (4F2hc/SLC3A2 or rBAT/SLC3A1) to form the heteromeric amino acid transporters (HAT). Six SLC7 family members are covalently linked by a disulfide bridge to 4F2hc: LAT1/SLC7A5, LAT2/SLC7A8, y^+LAT1/SLC7A7, y^+LAT2/SLC7A6, Asc-1/SLC7A10, and xCT/SLC7A11[4–6] (reviewed in Palacín et al.[7]) (see Table 1). The heavy chain 4F2hc is required for the stability of the transporter at the plasma membrane, whereas the light chain (e.g., LAT1) facilitates amino acid transport across the membrane.[2] Thus, substrate selectivity and ion transport are mediated by the light chain (e.g. LAT1). Based on these transporter properties, HATs can be further subgrouped (see Table 1): System L (LAT1–4F2hc, LAT2–4F2hc), system y^+L (y^+LAT1–4F2hc, y^+LAT2-4F2hc), system x_c^- (xCT–4F2hc), and system ASC (Asc-1-4F2hc) (reviewed in Fotiadis et al.[2]). System L (leucine preferring) transporters are Na^+-independent and mediate the uptake of neutral L-amino acids. System y^+L transporters transport cationic or neutral amino acids, dependent on the ionic composition of the environment. The transport of cationic amino acid is Na^+ independent, while the transport of neutral amino acids is Na^+ dependent. System x_c^- transporters are Na^+-independent anionic amino acid transporters, which facilitate the exchange of extracellular cystine with intracellular glutamate. System ASC transporters mediate the Na^+-dependent exchange of small, neutral amino acids.

One of the best characterized HATs is the system L transporter LAT1–4F2hc.[2,4,5] LAT1–4F2hc mediates the cellular uptake of large neutral amino acids such as leucine, isoleucine, valine, phenylalanine, tyrosine, tryptophan, histidine, and methionine in a Na^+-independent manner.[4,30,31] The cellular uptake of one amino acid is coupled to the export of another amino acid (histidine, glutamine, or tyrosine) by the same LAT1–4F2hc transporter. Hence, LAT1–4F2hc exchanges amino acids across membranes.[6] It also transports amino acid derivatives, including L-DOPA (L-3,4-dihyroxyphenylalanine),[8] thyroid hormones[9] and drugs, such as gabapentine.[32,33]

LAT1–4F2hc is expressed in many different cells, but the expression levels differ among tissues and cell types. LAT1–4F2hc is highly expressed at the plasma membrane of brain capillary endothelial cells in the blood–brain barrier (BBB),[10,11] or in the inner blood–retinal barrier (BRB),[12] as well as in syncytiotrophoblast cells in placental membranes,[9,13] and in activated immune cells[14,15] (reviewed in Ren et al.[34]).

It is generally assumed that LAT1–4F2hc is important to satisfy the increased demand of amino acids of proliferating cells in pathophysiological settings but also under physiological conditions. Consistently, LAT1–4F2hc is essential for embryogenesis to support the metabolic demands of morphogenesis[35] and its loss is embryonic lethal.[35–37] LAT1-deficient embryos cannot develop beyond mid-gestation, which is the point when nervous cells start to differentiate.[38] Moreover, LAT1–4F2hc is also frequently upregulated/overexpressed in cancer cells (reviewed in Kanai[39]).

3 | STRUCTURE OF THE HUMAN LAT1–4F2hc COMPLEX

High-resolution structural models of the human LAT1–4F2hc complex were obtained by cryo-electron microscopy.[30,40] LAT1 consists of 12 transmembrane domains (TMDs) (Figure 1). Ten core TMDs, with a "5 + 5"

TABLE 1 Amino acid transporter systems in the heteromeric amino acid transporters (HAT)

Heterodimeric amino acid (HAT) transporters				
System	**Name**	**Substrates**	**Transport method**	**References**
L	LAT1 (SLC7A5)	Large, neutral AA, L-DOPA, thyroid hormones	Exchanger, 1:1 stoichiometry, Na^+-independent	8–15
	LAT2 (SLC7A8)	Smaller, neutral AA		16–19
y^+L	y^+LAT1 (SLC7A7)	Cationic AA, large neutral AA	Exchanger, cationic AA Na^+-independent, neutral AA Na + -dependent	20–23
	y^+LAT2 (SLC7A6)			22–24
x_c^-	xCT (SLC7A11)	Cystine, glutamate	Exchanger, 1:1 stoichiometry, Na^+-independent	25–27
ASC	Asc-1 (SLC7A10)	Small neutral AA	Exchanger, Na^+-independent	28,29

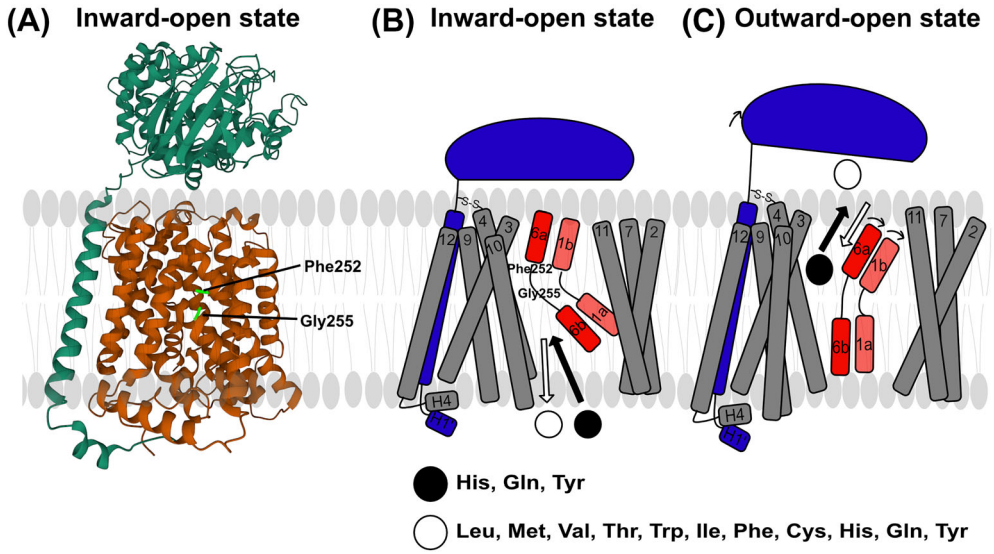

FIGURE 1 Cartoon of the structural model for LAT1–4F2hc. (A) Structural model of LAT1–4F2hc in an inward-open confirmation (model based on cryo-EM: PDB ID: 6IRT[30]) 4F2hc is depicted in green, LAT1 in orange and the residues Phe252 and Gly255 are highlighted in light green. (B) The cartoon depicts a possible transport mechanism of LAT1–4F2hc. In the inward-open state, substrates from the intracellular side are able to bind to LAT1, inducing the rotation of TM1a and TM6b towards the hash domain to close the gate. (C) In the outward-open state, TM1b and TM6a are further rotating, leading to substrate release. The extracellular domain of 4F2hc is also rotating, stabilizing LAT1 (model according to structural analysis from previous works[30,40,41]). 4F2hc is depicted in blue, parts of LAT1 are depicted in grew. TM6a and b of LAT1 are depicted in dark red, whereas TM1b and a are depicted in light red.

inverted repeat topology, form three functional subdomains, called hash, bundle, and arms. The bundle domain forms the substrate passageway with the conserved substrate-binding site. This architecture is similar to other APC (amino acid-polyamine organocation) family members.[40,42]

The human 4F2hc is a type II membrane N-glycoprotein with an intracellular N-terminus and a bulky extracellular C-terminus.[43] It is embedded in membranes with a single TMD.[44] This TMD interacts with TM4 of LAT1, probably already at the endoplasmic reticulum (ER), to facilitate transport to the plasma membrane as it is the case for b^{0+}AT–rBAT (SLC7A9–SLC3A1).[45] The large glycosylated extracellular domain of 4F2hc is connected to the membrane-spanning domain via a short linker. This linker is important for the heterodimer structure by forming disulfide bridges and hydrogen bonds with LAT1. The glycosylation of 4F2hc is not directly involved in the binding to LAT1.[40] In the structural models of the LAT1–4F2hc heterodimer, the large extracellular domain of 4F2hc is positioned, seemingly hovering, above LAT1 (Figure 1). In addition to disulfide bridges, 4F2hc interacts with LAT1 via several interfaces between the extracellular domains, the transmembrane domains, and the intracellular regions.[30,40] These interfaces are mainly formed by electrostatic interactions with the LAT1-facing surface of 4F2hc being mainly positively charged and with the 4F2hc-facing surface of LAT1 being mainly negatively charged.[40] The interaction of 4F2hc with LAT1 is essential for the stability of LAT1[4,46] and its proper localization at the plasma membrane (reviewed in Palacín and Kanai[47]). 4F2hc is also important for the amino acid transport activity of LAT1,[48,49] as disruption of polar interactions between 4F2hc and LAT1 on the extracellular side significantly reduces leucine uptake.[30]

4 | SUBSTRATE TRANSPORT AND SPECIFICITY OF LAT1–4F2hc

LAT1–4F2hc is an obligatory amino acid exchanger.[6] The import of one amino acid is coupled to the export of another amino acid in a 1:1 ratio.[2,50] Glutamine, histidine, and tyrosine are transported bidirectionally, whereas most of the other substrates (e.g., leucine and methionine) are preferentially imported[5,50] (reviewed in Kanai[39] and Puris et al.[51]). LAT1–4F2hc also displays an asymmetry in apparent affinities for its substrates.[52] At the intracellular side, it has a lower affinity for amino acids compared to a high apparent affinity for extracellular substrates. It follows that the transport rates are mostly set by the concentration of intracellular exchange substrates. This bestows another property to LAT1–4F2hc: Due its bidirectional transport, it balances the proportional distribution of amino acids, rather than generating net amino acid import.[50,53] Therefore,

LAT1–4F2hc belongs to a group of amino acid transporters that is classified as "harmonizer."[54–56] Most of the mechanistic knowledge of substrate transport by LAT1 is based on findings on the LeuT fold of prokaryotic transporters (reviewed in Rullo-Tubau et al.[57] and Singh and Ecker[58]). While the human LAT1 and bacterial amino acid transporters share low sequence identity, they share the structurally conserved LeuT fold.[59] In contrast to its bacterial homologues, LAT1 is able to recognize a broader range of substrates and catalyses transport in a Na^+- and pH-independent manner.[4,60,61] The LAT1 bundle domain, formed by TM1, TM2, TM6, and TM7, is especially important for substrate binding.[40] TM1 and TM6 are disrupted by a short loop and thereby divided into two shorter helices: TM1a and TM1b and TM6a and TM6b.[30,40] In the so-called inward-open state, TM1a and TM6b form a solvent-exposed cavity towards the cytoplasmic side.[40,62] At the end of this gate is the substrate-binding site. The substrate binding site is composed of a positive pole in TM1b and a negative pole in TM6a, which mediate the recognition of the negatively charged carboxyl group and the positively charged amino moieties of the ligand.[32,40,63,64] Notably, a phenylalanine residue (Phe252) in TM6 has been shown to be critical for substrate binding through hydrophobic interactions.[62] Residues in TM1 are important in the substrate recognition through backbone interactions. A glycine residue (Gly255) in TM6 allows the ligands to access an additional pocket, called distal pocket, which can accommodate bulky hydrophobic side chains of the amino acid substrates.[64] Thereby, this distal pocket biases the substrate specificity towards large amino acids.[30,40,64] Consistently, the complex can transport a wide range of large neutral amino acids, including leucine, isoleucine, phenylalanine, tyrosine, tryptophan, methionine, and histidine with high affinity[65] (Figure 1). Notably, this distal pocket is not present in the bacterial transporters. Taken together, a unique combination of residues in the substrate binding site and differences in the confirmation of TM6 due to its interaction with surrounding TMs are key for the differences in substrate selectivity[66] and also determines the size of the substrates.[40]

Once the substrates are engaged, they are moved directionally across the membrane in the so-called "rocking bundle alternating-access" mechanism (reviewed in Singh and Ecker[58]), in which the transporter adapts different conformations to translocate the substrate across the plasma membrane. This model is well established for prokaryotic transporters. Based on the structure of LAT1–4F2hc, it is likely that the human complex follows a similar mechanism of amino acid transport.[40] In the inward-open state, the substrate binding site is accessible to the inside of the cell and closed to the extracellular space. The substrate (e.g., glutamine or histidine) binds at the cytosolic side of LAT1, causing the rotation of TM1a and TM6b towards the hash domain to close the inward gate. Subsequently, TM1a and TM6b continue to rotate, while TM1b and TM6a rotate away from the hash domain, leading to an outward-occluded state. Finally, TM1b and TM6a pushes Phe252 residue in the substrate binding pocket, triggering the outward-open state and substrate release. During this process, the extracellular domain of 4F2hc also undergoes a rotation, which appears to stabilize LAT1 and also facilitates local conformational shifts in the gating elements of LAT1[41] (Figure 1). In this outward-open state, extracellular amino acids (e.g., leucine) can engage LAT1 for cellular uptake.

5 | LAT1–4F2hc IS A KEY REGULATOR IN CELLULAR GROWTH

LAT1–4F2hc contributes to cell growth because it participates in the distribution of essential amino acids, which contribute to the activation of the master growth regulator, mTORC1. As amino acid "harmonizer," it also helps to maintain the concentration of intracellular BCAAs (branched chain amino acids, e.g., leucine, isoleucine, and valine). This function of LAT1–4F2hc is especially important in the brain, where those amino acids are crucial for normal development and function (reviewed in Yudkoff et al.[67]).

5.1 | The importance of LAT1–4F2hc in mTORC1 signalling

The link between mTORC1 and LAT1 is based on LAT1's ability to import the essential amino acid leucine.[61,68] mTORC1 is a conserved serine/threonine kinase signalling complex that regulates cellular growth[69,70] (reviewed in Liu and Sabatini[71] and Valvezan and Manning[72]). In the presence of growth factors and amino acids, mTORC1 is active and stimulates anabolic processes while inhibiting catabolic ones. The activity of mTORC1 can be directly regulated by free amino acids[73] (reviewed in Zheng et al.[74]). When free amino acids are abundant inside cells, mTORC1 is recruited to the surface of lysosomes and activated (Figure 2). The translocation to lysosomes is mediated by activated Rag GTPases, which are tethered to lysosomes by the LAMTOR complex (late endosomal/lysosomal adaptor and mTOR and MAPK activator).[75–77] The heterodimeric Rag GTPase family consists of Rag A (or Rag B) and Rag C (or Rag D).[78] The

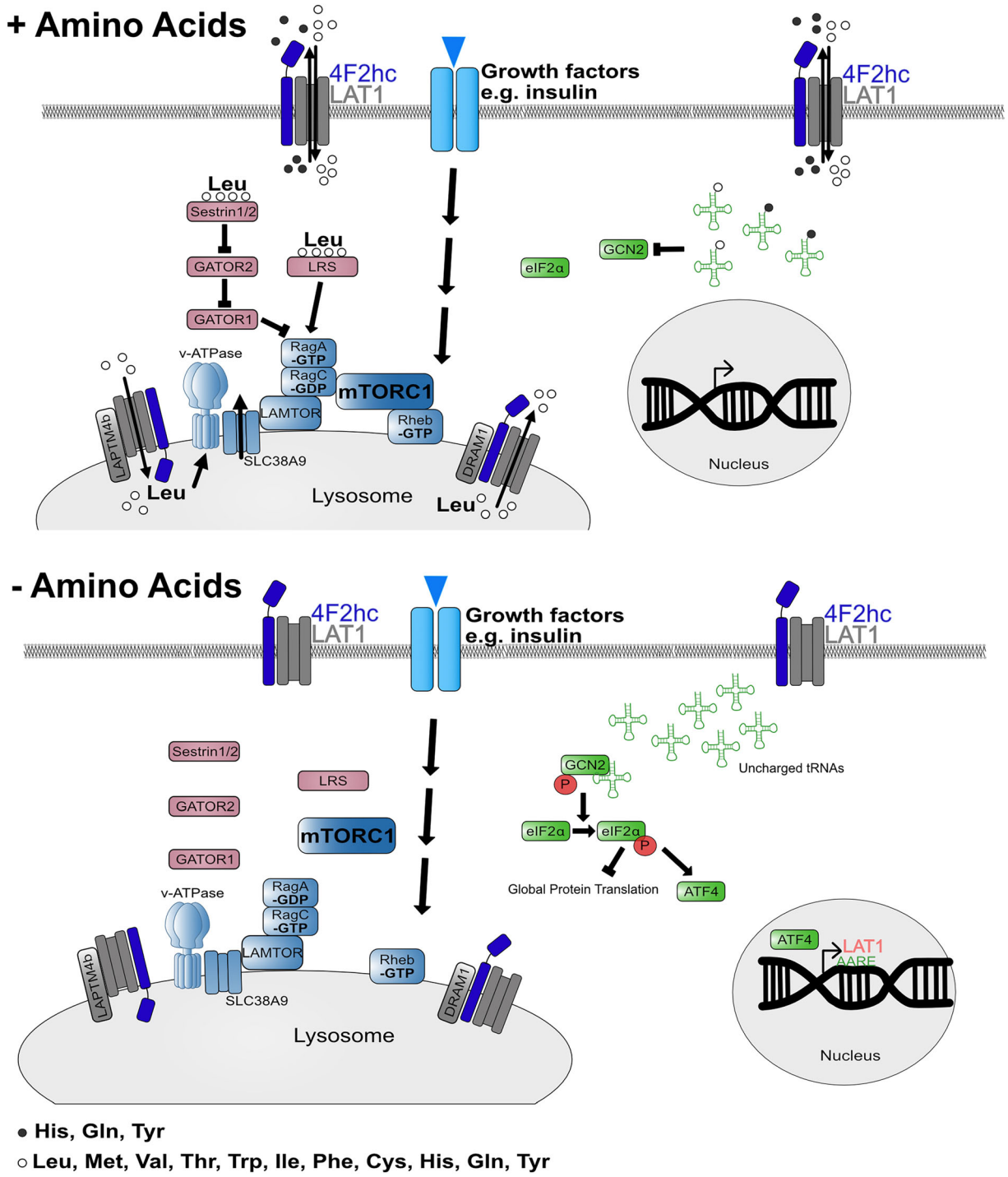

FIGURE 2 LAT1–4F2hc in mTORC1 signalling and the intergraded stress response. Cartoon showing components of the nutrient-sensing as well as growth factor sensing pathway upstream of mTORC1. LAT1–4F2hc mediated leucine uptake activates mTORC1 via the amino acid sensors Sestrin1/2 and LRS. The amino acid stress response pathway is part of the ISR. Amino acid deprivation induces the accumulation of uncharged tRNAs. Activated GCN2 phosphorylates eIF2α. In turn, global protein translation is inhibited and the transcription factor ATF4 is preferentially translated. ATF4 controls the expression of LAT1.

Rag A/C GTPase is activated when Rag A is GTP-bound and Rag C is GDP bound.[79] The activation status of the Rags is regulated by different free amino acids. Among those, the essential amino acid leucine is particularly important to activate mTORC1. Free leucine can bind to Sestrin1/2, causing their conformational changes, which leads to the dissociation of GATOR2 (GAP activity towards Rags complex 2).[80–82] GATOR2 is now able to

inhibit GATOR1, a conserved GAP (GTPase-activating protein) for Rag A/B. Consequently, the leucine-sestrin axis promotes Rag activation and mTORC1 signalling (reviewed in Valvezan and Manning[72]). Intracellular leucine concentrations can also be sensed by leucyl-tRNA synthetase (LRS). In the presence of leucine, LRS translocate to the surface of lysosomes, where they activate the Rags.[83–87] Once on lysosomes, mTORC1 can be further activated by GTP-bound Rheb (Ras homologue enriched in brain). Rheb is a GTPase, which is activated downstream of growth factor signalling.[88] Hence, when amino acids are plenty and when growth factors are present, mTORC1 is fully activated on the surface of lysosomes to promote cell growth (Figure 2).

Typically, LAT1–4F2hc transports extracellular leucine into the cytosol across the plasma membrane. Yet, when LAT1–4F2hc interacts with LAPTM4b (lysosomal-associated transmembrane protein 4b), it can also function at the limiting membrane of lysosomes. There, LAT1–4F2hc is capable to mediate the transport of leucine from the cytosol into lysosomes to additionally stimulate mTORC1 activation via v-ATPase (vacuolar H^+-adenosine triphosphatase).[89] Another study suggested that the lysosomal membrane protein DRAM-1 (DNA damage regulated autophagy modulator 1) guides LAT1–4F2hc to lysosomal membranes, where this complex then mediates amino acid export from the lysosome into the cytosol.[90] It will be interesting to further characterize the molecular mechanism that allow LAPTM4b and DRAM-1 to control LAT1–4F2hc transport activity across lysosomal membrane, particularly given that they could be directly related to mTORC1 signalling.

In addition to these lysosomal LAT1 complexes, the lysosomal membrane contains other amino acid transporters/sensors for amino acids that are directly coupled to mTORC1 signalling (e.g., SLC38A9 and v-ATPase).[91–93] How LAT1-mediated amino acid transport across the plasma membrane and lysosomes differs in its capability to regulate mTORC1 remains to be determined. Regardless, it is already clear that pharmacological LAT1 inhibition or genetic LAT1 deletion decreases mTORC1 activity.[94–97] Conversely, mTORC1 upregulates LAT1–4F2hc expression, whereas mTORC1 inhibition suppresses *LAT1* and *4F2hc* mRNA expression.[98]

5.2 | LAT1–4F2hc and the integrated stress response (ISR)

Another major sensor of intracellular amino acids is the protein kinase GCN2 (general control nondepressible 2), which is one of four branches of the ISR. The ISR is a conserved signalling network that reacts to different stresses, including amino acid deprivation, protein folding stress in the ER, iron/heme deficiency, and viral infection (dsRNA). These stresses are sensed by specialized kinases (GCN2, PERK, HRI and PRK) that—once activated—phosphorylate the eukaryotic translation initiation factor eIF2α. eIF2α phosphorylation suppresses global protein synthesis and, simultaneously, induces the selective translation of some mRNAs (reviewed in[99]). Amino acid deprivation and the ensuing occurrence of uncharged tRNAs and ribosomal stalling activate the GCN2 branch of the ISR.[100,101] Phosphorylated eIF2α then downmodulates general translation but, at the same time, induces the translation of the transcription factor ATF4. ATF4 induces the transcription of its target genes by binding to amino acid response elements (AARE) in their DNA sequences, to the effect that genes are transcribed that help the cell to overcome the amino acid depletion.[102] Of note, the first intron of LAT1 contains a conserved AARE and increased ATF4-mediated transcription of *LAT1* is observed upon leucine and glutamine deprivation[103,104] (Figure 2). Increased phosphorylation of GCN2 and activation of the ISR is further observed upon inhibition or deletion of LAT1.[95,96] Conversely, GCN2 can promote the growth of prostate cancer cells by up-regulating the expression of LAT1 (and 60 other amino acid transporters) and thereby maintaining amino acid homeostasis.[105] Consistently, GCN2 or ATF4 deficient cells are impaired in expressing genes involved in amino acid import (including LAT1 but also others)[102] and are more sensitive to nutrient deprivation, but also to oxidative stress and other triggers that would result in ISR activation.

6 | LAT1 AND RELATED DISEASES

Overexpression or loss of LAT1–4F2hc function are linked to several human pathologies (reviewed in Scalise et al.[106]).

6.1 | LAT1 and cancer

The impact of LAT1 in cancer has been summarized in excellent reviews.[39,107,108] Increased expression levels of LAT1–4F2hc often correlate with high proliferating rates in a wide range of cancer cell lines,[109] primary human cancers, angiogenesis, and metastases. High LAT1–4F2hc expression is thought to match the increased demand of proliferating cells for essential amino acids for energy supply, protein synthesis, and to induce hyperactivation of mTORC1, thereby re-enforcing cell growth. In some instances, LAT1–4F2hc expression is used as prognostic

marker, as high expression is linked to poor diagnosis in non-small cell lung cancer, triple negative breast cancer and prostate cancer.[110–115] Cancer-specific overexpression of LAT1 can also be exploited for positron emission tomography (PET) to visualize tumours in cancer patients. F-labelled FAMT (3-fluoro-L-α-methyl-tyrosine) is a LAT1-specific PET probe that accumulates specifically in tumours with low physiological background.[116,117] LAT1 overexpression has also been associated with chemotherapy resistance[118,119] and with cancer proliferation after chemotherapy.[118,120] In these settings, LAT1 (as a transporter protein) may influence the cellular uptake and release of drugs in cancer cells, leading to reduced sensitivity in chemotherapy.

The transcriptional up-regulation of LAT1–4F2hc in transformed cells involves oncogenic transcription factors. c-Myc can bind to the promoter of *LAT1*, leading to increased expression in cancer cells.[121,122] This activates a regulatory feedforward loop, as LAT1-mediated uptake of essential amino acids, in turn, stimulates *Myc* mRNA translation partly via attenuation of the GCN2-mediated ISR.[122,123] Likewise, the hypoxia-inducible factor 2α (HIF2α) is able to bind to the *LAT1* proximal promoter, also inducing its expression.[124,125] The hippo pathway effectors YAP/TAZ, two transcriptional regulators that form a complex with the transcription factor TEAD, directly increases transcription of *LAT1*, subsequently leading to high LAT1 activity.[126] Oncogenic KRAS stabilizes YAP1 and thereby upregulates LAT1 to support cancer cell proliferation.[127,128] In some cancer cell lines, the aryl hydrocarbon receptor (AHR), a transcription factor that is regulated by environmental toxicants, can induce *LAT1* expression.[129,130]

Not only LAT1 but also 4F2hc has been associated with cancer progression (reviewed in Cantor and Ginsberg[131]). 4F2hc not only associates with amino acid transporters, but it is also able to associate with integrin-β chains,[132–134] thereby influencing integrin signalling and thus, cell survival and cell migration.[135]

6.2 | LAT1 function in the immune system

The important role of LAT1 in T cell development, activation and differentiation is well established (reviewed in[108]). LAT1–4F2hc is essential for the clonal expansion and/or differentiation of T cells into $CD4^+$/$CD8^+$ effector cells.[14,136] Consistently, the mRNA expression levels of *LAT1–4F2hc* increases in T cells, that are activated by the TCR (T cell receptor) or by cytokines.[137,138] The upregulation of LAT1–4F2hc is also observed during the activation of other types of immune cells (reviewed in[108]). Thus, the transporter complex might contribute to inflammation and inflammatory diseases. Indeed, pharmacological inhibition of LAT1 suppresses Th2 (T helper 2) cell-mediated dermal inflammation[139] and allergic rhinitis (hay fever) in mice.[140] Since LAT1 promotes mTORC1 signalling, its role in inflammation is, at least in part, mediated by stimulation/activation of mTORC1 activity.[138,141] Thus, pharmacological inhibition of LAT1 might lead to ambiguous effects. It might benefit in therapy of autoimmune and inflammatory diseases, but also exhaust the active immune cells in other diseases such as cancer. Interestingly, preclinical and clinical trials using LAT1 inhibitors in cancer therapy have not yet reported signs of immunosuppression or exhaustion.[142]

6.3 | LAT1 and insulin resistance/type 2 diabetes (T2DM)

Branched chain amino acids (BCAAs) are substrates of LAT1–4F2hc. The plasma concentrations of BCAAs are typically decreased during fasting. Increased plasma concentrations of BCAAs during fasting, correlate with metabolic diseases including obesity, insulin resistance or type 2 diabetes mellitus (T2DM)[143,144] (reviewed in Lynch and Adams[145]). The underlying molecular mechanism is not fully understood and several models propose a mechanistic rational for this correlation (discussed in Lynch and Adams[145] and White et al.[146]). One hypothesis proposes that LAT1-mediated uptake of BCAAs activates mTORC1 in a coordinated manner together with insulin signalling. Consistently, hyperactivation of mTORC1 is linked to obesity and T2DM (reviewed in Ardestani et al.[147]). In mouse pancreatic β-cells, increased amino acid uptake mediated by LAT1 correlates with increased insulin biosynthesis and secretion.[148,149] Moreover, insulin upregulates *LAT1* expression in mouse skeletal muscle cells.[150] Glucose, however, has been reported to have different effects on *LAT1* expression levels. In one study, high glucose concentrations on myocytes reduced *LAT1* mRNA levels via inactivation of AMPK signalling. This finding led to the hypothesis that the import of BCAAs into cells by LAT1–4F2hc is reduced in the presence of high glucose, which then could result in the increased blood levels of BCAA in diabetes patients.[151] One far reaching consequence of such increased plasma BCAA concentrations might be competition with the uptake of neurotransmitter via LAT1–4F2hc across the BBB.[152,153] Thereby, LAT1–4F2hc might also contribute to increased hunger in obese patients or to depression. Another study reported that in retinal capillary endothelial cells, glucose deprivation induces *LAT1* and *4F2hc* mRNA.[154] Clearly, the role of LAT1–4F2hc in the occurrence and

development of insulin resistance, T2DM, and obesity needs to be further clarified.

6.4 | LAT1 and neurological diseases

Tissue-specific deletion of LAT1 from the BBB results in an abnormal amino acid profile in the brain, which leads to the activation of the GCN2-mediated ISR and causes autism-related phenotypes in mice. Thus, LAT1 is essential for brain metabolism and development (reviewed in Errasti-Murugarren and Palacín[155]). Consistently, mutations in the genes encoding *LAT1* or *4F2hc* can cause neurological disorders. Whole exome sequencing data identified two homozygous mutations (Ala246Val and Pro375Leu) in the *LAT1* gene in two independent families with affected individuals suffering from autism spectrum disorder and motor delay. The Ala246Val mutation changes a highly conserved alanine situated in the N-terminal part of TM6a, affecting ligand transport. Pro375-Leu is located in TM9, also reducing leucine uptake.[156] Besides BCAAs, LAT1–4F2hc also transports the dopamine precursor L-DOPA across the BBB.[8] One hypothesis is that BCAAs compete with L-DOPA for LAT1–4F2hc-mediated transport (reviewed in Beckers et al.[157]). This could be an important aspect in the treatment of Parkinson's disease. L-DOPA is administered orally for treatment, but many patients develop resistance during the course of therapy.

LAT1–4F2hc might also be used to deliver drugs or prodrugs across the BBB (reviewed in[51]). One such example is gabapentin, a drug that is used in the treatment of epilepsy and neuropathic pain.[33] Thus, a better understanding of the function and regulation of LAT1–4F2hc might help to develop better treatment of neurological diseases.

7 | PHARMACOLOGICAL MODULATION OF LAT1–4F2hc ACTIVITY

Based on the context-dependent function of LAT1, specific drugs that stimulate or inhibit its transport activity could provide valuable therapeutic options in the above-mentioned diseases. Drugs that inhibit LAT1 function have been generated. Since LAT1–4F2hc is highly expressed in various cancer tissues and required for cancer cell growth and proliferation,[95,158] it could be an ideal target for cancer and immune regulatory therapy (reviewed in Kanai[39] and Zhang et al.[107]). Most of the LAT1–4F2hc inhibitors are amino acid derivatives and some are potent and selective (reviewed in Singh and Ecker[58]). The most advanced compound JPH203 (also called KYT-0353), a tyrosine analogue,[159] is currently being evaluated in Phase II clinical trial in patients with advanced biliary tract cancers (UMIN000034080).[142] JPH203 suppresses cell proliferation in various types of cancer. The underlying molecular mechanisms are not fully clear, but one hypothesis is that JPH203 treatment inhibits amino acid uptake and thereby starves proliferating cells. This would activate the amino acid stress response and supress mTORC1 signalling.[95] Consistently, phospho-proteomic data also revealed that JPH203 treatment inactivates cell cycle-related kinases and proteins, thereby inducing cell cycle arrest in different cancer cell lines.[160] Tissue culture experiments further demonstrate that long-term treatment with JPH203 does not induce resistance to LAT1 inhibition in medulloblastoma cells.[94] However, a compensatory upregulation of other transporters or adaption of signalling pathways could potentially weaken JPH203 efficiency. Since LAT1–4F2hc mediated uptake of BCAA is important for the activation of immune cells, inhibition of LAT1-4F2hc might blunt immune responses. Inhibition of LAT-14F2hc might also affect transport across the BBB with consequence on brain function. Therefore, potential side effects of JPH203 treatment on brain metabolism and the immune system need to be carefully evaluated. First preclinical trials using JPH203 as anticancer treatment have not reported signs of immunosuppression.[94] Another important aspect in LAT1–4F2hc-targeted disease therapy is that other drugs might also affect LAT1 expression. For instance, FTY720 (fingolimod), which is used to treat multiple sclerosis, induces LAT1 ubiquitination and endocytosis in HeLa cells.[161,162]

7.1 | Conclusions

Here, we have briefly discussed how LAT1–4Fhc2 dysfunction contributes to the pathophysiology of cancer, diabetes, and neurological diseases. The basic knowledge of LAT1–4F2hc structure and function is continuously improving and several transcriptional mechanisms have been identified that upregulate LAT1–4F2hc expression. Yet, it should be noted that changes in mRNA levels of *LAT1–4F2hc* does not always reflect transporter activity of LAT1–4F2hc at the plasma membrane or on lysosomes. Moreover, it is currently unclear if and how LAT1–4F2hc is regulated on post-translational level. In particular, we do not know how cells control LAT1–4F2hc localization at the plasma membrane or on lysosomes to harmonize amino acid uptake. Answers to this question would provide novel aspects for

LAT1–4F2hc regulation with novel therapeutic windows to stimulate or inhibit LAT1–4F2hc function or to redirect LAT1–4F2hc activity from the plasma membrane to lysosomes.

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CONFLICT OF INTEREST

The authors declare there are no conflict of interest.

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