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DRUG METABOLISM & DISPOSITION

Special Section on New Era of Transporter Science: Unraveling the Functional Role of Orphan Transporters—Minireview

Amino Acid Solute Carrier Transporters in Inflammation and Autoimmunity

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ABSTRACT

The past decade exposed the importance of many homeostasis and metabolism related proteins in autoimmunity disease and inflammation. Solute carriers (SLCs) are a group of membrane channels that can transport amino acids, the building blocks of proteins, nutrients, and neurotransmitters. This review summarizes the role of SLCs amino acid transporters in inflammation and autoimmunity disease. In detail, the importance of Glutamate transporters SLC1A1, SLC1A2, and SLC1A3, mainly expressed in the brain where they help prevent glutamate excitotoxicity, is discussed in the context of central nervous system disorders such as multiple sclerosis. Similarly, the cationic amino acid transporter SLC7A1 (CAT1), which is an important arginine transporter for T cells, and SLC7A2 (CAT2), essential for innate immunity. SLC3 family proteins, which bind with light chains from the SLC7 family (SLC7A5, SLC7A7, and SLC7A11) to form heteromeric amino acid transporters, are also explored to describe their roles in T cells, Natural Killer (NK) cells, macrophages, and tumor immunotherapies. Altogether, the link between SLC amino acid transporters with inflammation and autoimmunity may contribute to a better understanding of underlying mechanism of disease and provide novel potential therapeutic avenues.

SIGNIFICANCE STATEMENT

In this review, we summarize the link between SLC amino acid transporters and inflammation and immune responses, especially SLC1 family members and SLC7 members. Studying the link may contribute to a better understanding of related diseases and provide potential therapeutic targets useful to the researchers who have interest in the involvement of amino acids in immunity.

Introduction

Nearly half of all deaths worldwide are attributed to chronic inflammatory conditions (Furman et al., 2019). In fact, one in every five Americans suffer from at least one chronic inflammatory condition and 3%–5% of an autoimmunity disorder (Wang et al., 2015). Traditionally, inflammatory and metabolic diseases were often approached separately, but the past decades have highlighted the importance of metabolic dysbiosis in chronic inflammation and autoimmunity disorders (Pitt et al., 2000; Sospedra and Martin, 2005; Compston and Coles, 2008). For example, multiple sclerosis (MS) is exacerbated by excessive glutamate transport and excitotoxicity, mediated by SLC proteins. Similarly, L-arginine transport, also mediated by SLCs, regulates multiple innate inflammatory mechanisms such of arginase-1 activity and inducible nitric oxide synthase (iNOS, NOS2).

The SLC superfamily is a large group of membrane transporters with over 65 families and more than 400 members. SLCs play important roles in nutrient and metabolic sensing (Chen et al., 2019; Zhang et al., 2019) and metabolic regulation of immune cells (Song et al., 2020). Structurally SLCs can be tremendously diverse with a myriad of substrates, and although several SLCs act as drug transporters (Liang et al.,

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ABBREVIATIONS: ASC, alanine serine cysteine; CAT, cationic amino acid transporter; CCL5, chemokine (C-C motif) ligand 5; CD, Cluster of differentiation; c-Myc, transcriptional regulator Myc-like; CNS, central nervous system; CX, connexin; EAAT, excitatory amino acid transporter; EAE, encephalomyelitis; GS, glutamine synthetase; HERV, human endogenous retrovirus; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; IFN, interferon; IL, interleukin; iNOS, NOS2, inducible nitric oxide synthase; LAT, L-type amino acid transporter; LPI, lysinuric protein intolerance; LPS, lipopolysaccharide; MDSC, myeloid-derived suppressor cell; MS, multiple sclerosis; mTORC1, mechanistic target of rapamycin complex 1; NF-κB, nuclear factor kappa B; NK, Natural Killer; NO, nitric oxide; SLC, solute carrier; TCR, T cell receptor; TLR, Toll-like receptor; TNF-α, tumor necrosis factor α; UC, ulcerative colitis; X^-AG system, excitatory amino acid transporter; y^+ system, Na^+-Independent Cationic Amino Acid Transporter; y^+L, lysine-preferring agency.

TABLE 1

SLC1 and SLC7: two amino acid solute carrier transporter families related to inflammation and autoimmunity
For detailed information about the SLC genes, please visit: http://www.bioparadigms.org.

Human Gene Name	Protein Name	Aliases	Substrates	Transport Type/ Coupling Ions	Tissue Distribution and Cellular/ Subcellular Expression	Relevant Molecular Mechanisms	Sequence Accession ID
SLC1A1	EAAC1, EAAC3	System X^-_{AG}	Glutamate, asparagine	C/Na^+, H^+, and k^+	Brain (neurons), lung, colorectal, kidney, liver, heart, placenta	IFN-β production: NF-κB pathway	NM_004170
SLC1A2	GLT1, EAAT2	System X^-_{AG}	Glutamate, asparagine	C/Na^+, H^+, and k^+	Brain (astrocytes, bergmann glia, neurons), liver, pancreas	Akt/mTORC pathway: NF-κB pathway	NM_004171 NM_001195728 NM_001252652
SLC1A3	GLAST, EAAT1	System X^-_{AG}	Glutamate, asparagine	C/Na^+, H^+, and k^+	Brain (astrocytes, bergmann glia), heart, skeletal muscle, placenta	NF-κB; IGF-1; TLR-3; IFN-β	NM_004172 NM_001166695 NM_001166696
SLC1A4	ASCT1, SATT	System ASC	Cystine, serine, L-Threonine	C/Na^+, E/amino acids	Widespread	iNOS	NM_003038 NM_001193493
SLC1A5	ASCT2, AAAT	System ASC	Asparagine, glutamine	C/Na^+, E/amino acids	Adipose tissue, lung, skeletal muscle, large intestine, kidney, testis	Lck phosphorylation; TCR signaling; NKG2D; IFN-γ production and degranulation	NM_005638 NM_001145144 NM_001145145
SLC7A1	CAT-1	System y^+	Arginine, lysine, ornithine	F (non-obligatory E)	Ubiquitous except for liver and lacrimal gland/ basolateral and intracellular membranes in epithelial cells	mTORC1 activity	NM_003045
SLC7A2	CAT-2	System y^+	Arginine, lysine, ornithine	F	CAT-2A: liver, skeletal muscle, pancreas; CAT-2B: inducible in many cell types	NO production; NF-κB pathway	NM_003046 NM_001008539
SLC7A5	LAT1	System L	Glutamine, leucine, methionine, tryptophan	E (similar intra- and extracellular selectivities, lower intracellular apparent affinity)	Brain, ovary, testis, placenta, spleen, colon, blood-brain barrier, fetal liver, activated lymphocytes, tumor cells	c-Myc expression; IFN-γ production and granzyme B expression	NM_003486
SLC7A7	y^+LAT1	system y^+L	Lysine, arginase, ornithine, methionine, leucine	Na^+ dependent transport of extracellular large neutral L-amino acids	Small intestine, kidney, spleen, leukocytes, placenta, lung/ basolateral in epithelial cells	NO production; NF-κB pathway	NM_003982
SLC7A11	xCT	system x_c^-	Cystine, glutamate	E (preferentially extracellular cystine against intracellular glutamate)	Macrophages, brain, retinal pigment cells, liver, kidney/ basolateral in epithelial cells	Glutathione production; ROS accumulation; mTOR and NFAT activity; glycolysis and glutaminolysis	NM_014331

Akt, protein kinase B; ASCT, alanine serine cysteine transporter; C, cotransporter; E, exchanger; F, facilitated transporter.; IGF, Insulin-Like Growth Factor; NFAT, nuclear factor of activated T cells; NKG2D, natural killer group 2, member D; xCT, Solute Carrier Family 7 Member 11; x_c^-, cystine/glutamate antiporter.

2015), many others can transport amino acids across membranes, such as members of SLC1 and SLC7 families (Table 1).

The SLC1 family of transporters, named high affinity glutamate and neutral amino acid transporter family, comprises five excitatory amino acid transporters (EAATs, also known as system X^-_{AG}) of the X^-_{AG} system and two alanine serine cysteine transporters (ASCTs) of the alanine serine cysteine (ASC) system. The ASC system includes the two neutral amino acid transporters of the SLC1 family, SLC1A4 (ASC transporter 1) and SLC1A5 (ASC transporter 2) (Kanai et al., 2013). The X^-_{AG} system includes SLC1A1 (EAAC1), SLC1A2 (GLT1, EAAT2), SLC1A3 (GLAST, EAAT1), SLC1A6 (EAAT4), and SLC1A7 (EAAT5), which are high affinity glutamate transporters responsible for L-glutamate and D/L-aspartate uptake with cotransport of three sodium ions (Na^+) and one proton (H^+) and counter-transport of one potassium ion (K^+)(Kanai et al., 2013). In the brain, SLC1A1 is mainly expressed in neurons; SLC1A2 in astrocytes, Bergmann glia, and neurons; and SLC1A3 in astrocytes and Bergmann glia (Kanai et al., 2013), all with important functions in the central nervous system (CNS) (Fig. 1).

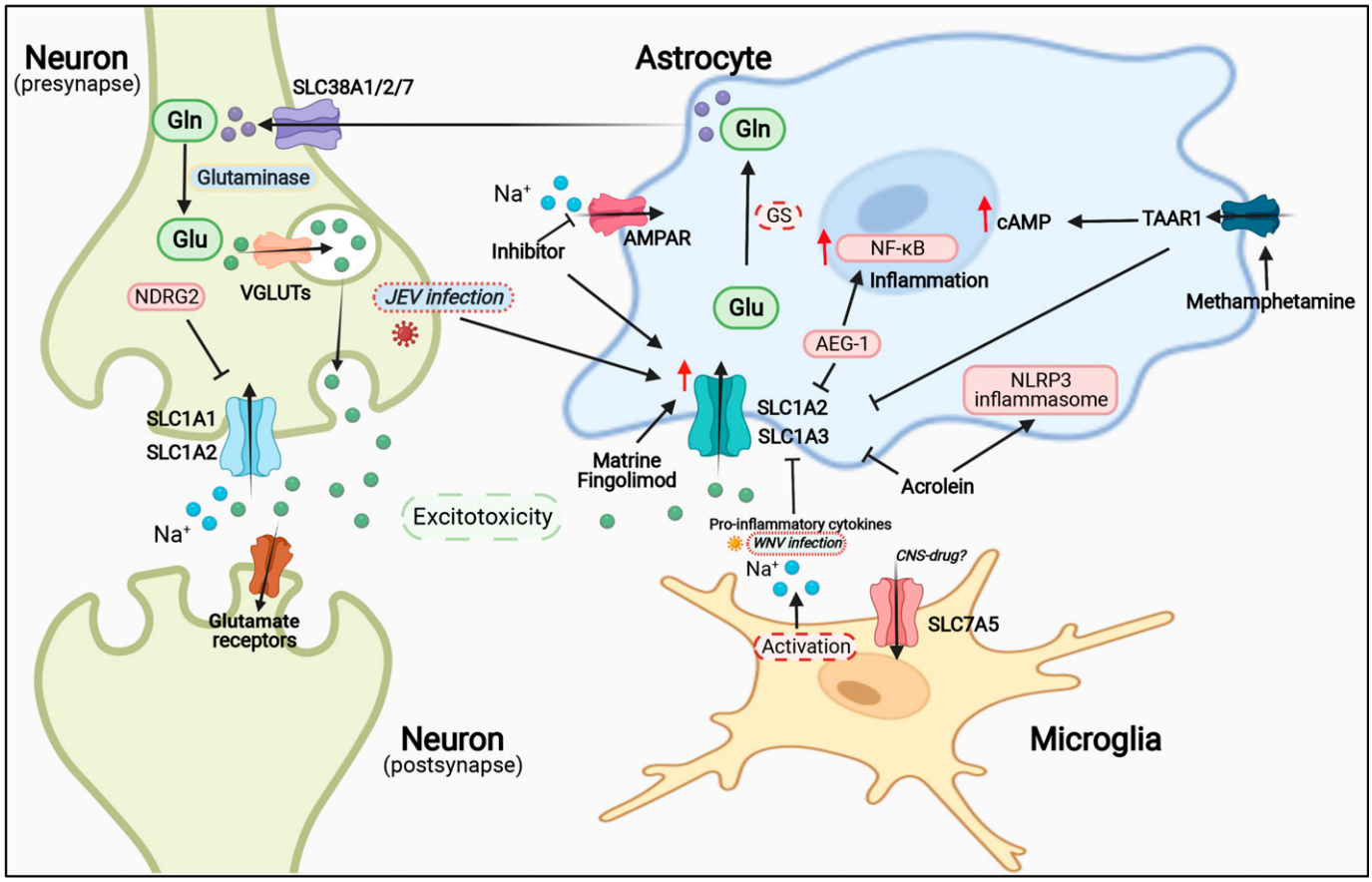

Fig. 1. Proposed roles of SLC1A1, SLC1A2, and SLC1A3 in the CNS. In neurons, glutaminase catalyzes the breakdown of glutamine (purple circle) to glutamate (green circle), which is transported illlllnto vesicles by VGLUTs and released into the synaptic space. SLC1A1, SLC1A2 reuptake glutamate into neurons, and SLC1A2, SLC1A3 uptake glutamate into astrocytes, preventing excitotoxicity. Astrocytic glutamine is synthesized from glutamate catalyzed by GS, and then used by neurons. Agents that have been reported to stimulate or inhibit SLC1A1, SLC1A2, and SLC1A3 are presented. Microglia upon activation releases glutamate. VGLUTs, vesicular glutamate transporters.

The SLC7 family of transporters, named cationic amino acid transporter/glycoprotein-associated family, are divided into two subfamilies: the cationic amino acid transporters (CATs) and the L-type amino acid transporters (LATs). CATs include SLC7A1-4 and SLC7A14, which mediate Na^+ independent transport of cationic L-amino acids (Fotiadis et al., 2013), whereas LATs are the light or catalytic subunits of heteromeric amino acid transporters (HATs) with a broad spectrum of substrates (Fotiadis et al., 2013), which are linked to the heavy subunits 4F2hc(SLC3A2) or rBAT(SLC3A1) through disulfide bonds. SLC7 transporters are important metabolic regulators in immune cells as summarized in Fig. 2.

In this review, the role of SLCs amino acids transporters in inflammation and autoimmunity and its supporting literature is discussed in detail. First, the part of SLC7 family members in innate and adaptive immune cells is debated, followed by the importance of SLC1 family proteins in neural inflammation, particularly in MS. Similarly, the role of SLCs in viral and bacterial infections is also analyzed, along with a brief summary on the impact of SLCs in other inflammatory disorders. Finally, the prospect of SLC based therapeutics is explored.

SLCs Function in Innate and Adaptive Immune Cells. The immune system is a complex biologic network traditionally separated in innate and adaptive immune cells. Innate immune cells such as Macrophages, Dendritic cells, and NK cells are generally the first responders, driving inflammation through antigen-independent mechanisms. Adaptive immune cells, such as T and B cells, are activated by innate immune signals and drive antigen-specific memory immunity.

SLC7A2 is highly involved in both innate and adaptive immunity. *Slc7a2* expression was induced in both classic (M1) and alternative (M2) activated in macrophages, and *Slc7a2* knockout blocked arginine transport and limited its activity after macrophage activation (Yeramian et al., 2006). Furthermore, Platonin, an inhibitor of acute inflammation, lowered nitric oxide (NO) production and arginine transport in lipopolysaccharide (LPS) stimulated mouse macrophages via iNOS and SLC7A2 inhibition (Chen et al., 2006). *Slc7a2* expression in peripheral monocytes was also found to be upregulated in pregnancy and was higher in preeclampsia, during which systemic inflammation is widespread and the arginine transport is strengthened (McCord et al., 2006). The lung of SLC7A2 deficient mice shows signs of spontaneous inflammation accompanied by increased dendritic cell (DC) and alveolar macrophages activation, but with compromised NO production (Rothenberg et al., 2006). Finally, myeloid-derived suppressor cells (MDSCs) suppressed T cell activities under inflammation or tumor conditions through increased arginine metabolism, whereas SLC7A2 deficiency promoted antitumor immunity (Cimen Bozkus et al., 2015).

Epithelial and endothelial cells also contribute for early innate inflammatory signals. In endothelial cells, human umbilical vein endothelial cells (HUVEC) stimulated by tumor necrosis factor α (TNF-α) showed higher *Slc7a2* expression (Knyazev et al., 2018); similarly, human saphenous vein endothelial cells (HSVEC) stimulated by TNF-α

showed elevated *SLC7A2* potentially via the nuclear factor kappa B (NF-κB) pathway, despite no effect on *Slc7a1* (Visigalli et al., 2004).

SLC7A7 also affects amino acid transport, differentiation, and immune function of macrophages. *Slc7a7* mRNA, SLC7A7 protein levels, and arginine transport were increased during monocyte differentiation to macrophages mediated by protein kinase C (PKC) activation. Contrastingly, the Na^+-Independent Cationic Amino Acid Transporter (y^+) system and lysine-preferring agency (y^+L) system mainly transported arginine and lysine outwards of macrophagic cells (Barilli et al., 2011). Silencing of *Slc7a7* in human Tohoku Hospital Pediatrics-1 (THP-1) macrophages and A549 epithelial cells induced secretion of interleukin-1β (IL-1β), TNF-α via the NF-κB pathway, and chemokine (C-C motif) ligand 5 /regulated upon activation normal T cell expressed and secreted factor (CCL5/RANTES) stimulated by IL-1β signaling feedback, which were independent of arginine concentration. Thus, *Slc7a7* likely plays a deeper role in inflammation aside of arginine transport (Rotoli et al., 2018). Mutation of *Slc7a7* could also cause lysinuric protein intolerance (LPI), in which arginine transport by system y^+L was impaired in macrophages and phagocytic activity was severely damaged (Barilli et al., 2012). In patients with LPI, plasma proinflammatory chemokines were higher, and LPI macrophages exhibited impaired response to Toll-like receptor 9 (TLR9) stimulation, higher response to TLR2/1 and TLR4 stimulation, and lower NO production (Kurko et al., 2015).

SLC7A5 mediated leucine transport in macrophages promoted mechanistic target of rapamycin complex 1 (mTORC1) signaling and proinflammatory cytokine production (Yoon et al., 2018). *Slc7a5* expression was upregulated in monocytes from rheumatoid arthritis patients and healthy monocytes after LPS stimulation. Additionally, *Slc7a5* expression levels positively correlated with rheumatoid arthritis clinical condition indicating a relationship of SLC7A5 with inflammation (Yoon et al., 2018). Similarly, a natural alkaloid piperine promoted mTORC1 signaling via recruitment of membrane SLC7A5/Cluster of differentiation 98 (CD98), synthesis of IL-6 and TNF-α, and phagocytic activity against bacteria in peritoneal macrophages (Pan et al., 2015). In activated NK cells, SLC7A5 also acted as a predominant amino acid transporter and together with glutamine supply was essential for maintaining transcriptional regulator Myc-like (c-Myc) and NK cell function (Loftus et al., 2018).

Still in macrophages, treatment with amphibole asbestos increased SLC7A11 expression, whereas SLC7A11 inhibition led to oxidative stress and cell death, which could be rescued by cysteine (Pfau et al., 2012). SLC7A11 was identified as a macrophagic host factor in the vesicular stomatitis virus replication (Kandasamy et al., 2016), and in LPS stimulated macrophages, SLC7A11 deficiency caused insufficient cysteine supply, decreased nitrite in the culture medium, and an increase in reactive oxygen species (Kobayashi et al., 2018). LPS stimulation in hippocampus elevated SLC7A11 expression, and knockout of SLC7A11 relieved peripheral and central inflammation and the effect of LPS stimulation in mice (Albertini et al., 2018). SLC7A11 was also elevated in IL-4-induced M2 macrophages during parainflammation and is related to M2 genes (Wang et al., 2020a).

SLC7A11 (Solute Carrier Family 7 Member 11, xCT) forms system cystine/glutamate antiporter (x_c^-) with CD98 and is mainly expressed in the brain, macrophages, and cell lines, and acts as a Na^+-independent transporter of extracellular anionic cystine and intracellular glutamate (Fotiadis et al., 2013). For T cells, although in vitro proliferation was SLC7A11-dependent, in vivo proliferation, immune response, and memory effects were SLC7A11-independent; therefore, using SLC7A11 as an antitumor therapeutic target should not affect T cell immune response (Arensman et al., 2019). Although baseline SLC7A11 levels are relatively low in T cells, thermal injury strongly induces SLC7A11, resulting in cystine import and T cell dysfunction (D'Elia et al., 2009). Glutathione production in part mediated by SLC7A11 can limit reactive oxygen species accumulation and support the activity of mTOR and nuclear factor of activated T cells to drive glycolysis and glutaminolysis in activated T cells (Mak et al., 2017).

In NK cells, IL-2 priming could upregulate SLC1A5 and SLC3A2 (CD98), which were both necessary for interferon γ (IFN-γ) production and degranulation by NK cells after stimulation of the activating receptor, natural-killer group 2 member D (Jensen et al., 2017). SLC1A5 participates in adaptive immunity as a conditionally essential glutamine transporter. SLC1A5-dependent rapid glutamine uptake occurred during naïve T cell activation, and SLC1A5 deficiency caused failure of Th1 and Th17 cell induction, as well as loss of the inflammatory T cell responses (Nakaya et al., 2014). Glutamine uptake through SLC1A5 and T cell receptor (TCR) signaling complex were both necessary for mTORC activation by TCR stimulation (Nakaya et al., 2014). Further, glucose and glutamine were both required upon B cell activation (Jiang et al., 2018). Overexpression of the microRNA cluster let-7adf reduced levels of both glucose by targeting hexokinase two and glutamate by inhibition of SLC1A5 and glutaminase, and further controlled antibody production of B cells (Jiang et al., 2018). However, *SLC1A5* knockout in mice was reported to have no influence on B cell development, proliferation, or function (Masle-Farquhar et al., 2017). Blocking SLC1A5 with L-γ-Glutamyl-p-nitroanilide (GPNA) to inhibit the uptake of glutamine can significantly enhance the inhibitory effect of cetuximab on the proliferation of gastric cancer and metastatic colorectal cancer in vivo and in vitro. Research provides the metabolic role of SLC1A5 as a potential therapeutic target to improve the efficacy of cetuximab for colorectal cancer and gastric cancer (Ma et al., 2018, 2021).

SLC7A1 seems to be the major system y^+ transporter in most cell types (Fotiadis et al., 2013). SLC7A1 expression was increased in $CD8^+$ T cells and naïve and memory $CD4^+$ T cells to provide sufficient arginine for T cell function (Werner et al., 2016). In contrast, *Slc7a1* expression was not induced by classic or alternative activation of macrophages (Yeramian et al., 2006). Meanwhile, *Slc7a5*$^{-/-}$ T cells showed impaired proliferation, differentiation, or metabolically reprogramming upon antigen stimulation, and leucine transport by L system was required for mTORC1 activity and c-Myc expression in activated T cells (Sinclair et al., 2013). The lack of methionine may also be responsible for the halt of protein production in *Slc7a5*$^{-/-}$ T cells, similar to the effect of *Myc* deletion (Marchingo et al., 2020). SLC7A5 inhibition as well as amino acid starvation triggered expression of homeobox B9 in activated T cells, which attenuated production of selective cytokines (Hayashi et al., 2016). SLC7A7 participated in the pathogenesis of T-cell acute lymphoblastic leukemia (Ji et al., 2018).

SLCs in Neural Inflammation and Autoimmunity (Multiple Sclerosis). Neurologic diseases afflict 3%–5% of the global population. Multiple sclerosis alone affects 59/100,000 habitants in Europe to a total of almost 700,000 people in 2017 (Deuschl et al., 2020). Transient inflammation and restorable neurologic dysfunction often occur during early MS stages, although widespread microglial activation and chronic neurodegeneration gradually develop (Compston and Coles, 2008). MS has traditionally been considered an autoimmune disease primarily mediated by $CD4^+$ Th1 cells, but other immune factors likely influence disease progression. SLC1A2 is expressed in astrocytes, neurons, and axonal terminals where it regulates glutamate concentrations in the CNS, often together with SLC1A3. Thus, these two transporters are mechanistically important in preventing excitotoxicity. In the inflammatory CNS microenvironment of MS, SLC1A3 and SLC1A2 levels and glutamate uptake were elevated in optic nerves and reduced

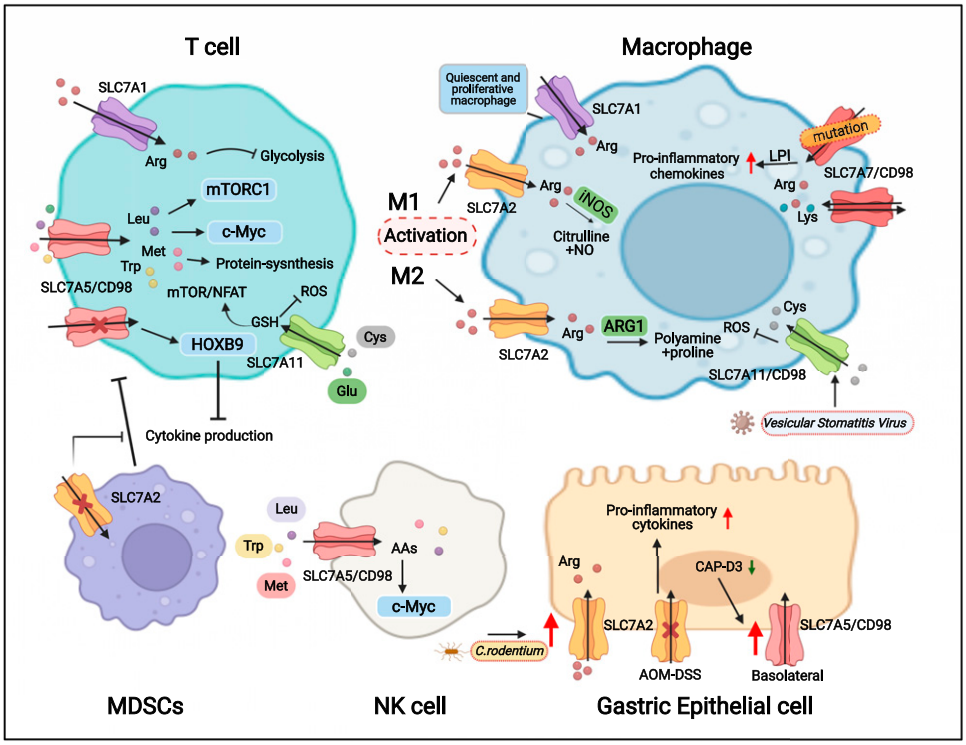

Fig. 2. Proposed roles of SLC7 transporters in immune cells. In T cells, SLC7A1 transports arginine; SLC7A5/CD98 transports leucine, methionine, tryptophan, and other amino acids; and SLC7A11 transports glutamate. Leucine is essential for mTORC1 activation and c-Myc maintenance, and methionine is necessary for protein synthesis. Suppression of T cells by MDSCs is abolished by SLC7A2 deficiency. GSH production in part mediated by SLC7A11 can limit ROS accumulation and support the activity of mTOR and nuclear factor of activated T cells to drive glycolysis and glutaminolysis in activated T cells. Leucine is also required for NK cells. In macrophages, M1 or M2 activation both induce SLC7A2/CD98-dependent arginine transport. Mutation of SLC7A7 causes LPI and lowers phagocytic activity and NO production of macrophages. SLC7A11/CD98 transports cysteine and could be induced by M2 activation. SLC7A2 deficiency in colon causes more severe AOM-DSS-induced colitis and favors M2 macrophage activation. UC reduced chromosome-associated protein D3 upregulating SLC7A5/CD98 expression. AAs, amino acids; AOM-DSS, azoxymethane-dextran sulfate sodium; GSH, glutathione; ROS, reactive oxygen species. * Figure created in biorender.com

excitotoxicity (Vallejo-Illarramendi et al., 2006). In cultured astrocytes, SLC1A3 and SLC1A2 levels were reduced after treatment with proinflammatory cytokines (Lee et al., 2017). In cortical lesions of MS brains, activated microglia correlated with decreased levels of SLC1A3, SLC1A2, and synaptophysin, and also elevation of phosphorylated-c-Jun N-terminal kinase levels in response of excitotoxicity (Vercellino et al., 2007). In the inflammation of MS, Th-17 cells function by releasing IL-17A, which promotes glutamate excitotoxicity by decreasing astrocyte SLC1A2, SLC1A3, and glutamine synthetase (GS) expression, and also by stimulating Ca^{2+}-dependent glutamate release, indicating an association between inflammation and neurodegeneration in MS (Kostic et al., 2017). In the early stages of neuroinflammation, glutamate released by activated microglia stimulated an increase in extracellular and intracellular glutamate levels of astrocytes and, in turn, resulted in reduced astrocytic SLC1A3 levels and failure of extracellular glutamate clearance (Takaki et al., 2012). SLC1A3 was also upregulated in the hypothalamus of long-living growth hormone receptor-knockout (KO) mice, together with higher expression of hypothalamic NF-κB, insulin like growth factor (IGF)-1 receptor, and the GluA1 subunit of the glutamate receptor; α-amino-3-hydroxy-5-methyl-4-isox-azolepropionic acid receptor (AMPAR) expression; and lower IL-1β in many brain regions. These data support the importance of decreased brain inflammation in early adulthood and maintained homeostasis of the glutamatergic and inflammatory systems in extended longevity (Hascup et al., 2016). In the brain, SLC7A11 participates in glutamate excitotoxicity mainly by controlling extracellular nonsynaptic glutamate concentration. Upon SLC7A11 upregulation by immune activation, extracellular glutamate rose and led to excitotoxicity (Pampliega et al., 2011).

Experimental allergic (autoimmune) encephalomyelitis (EAE) in mice is widely used as a demyelinating model for MS. After EAE induction, mice lacking N-Myc downstream-regulated gene 2 maintained more SLC1A3 and SLC1A2, and the inhibitory effect of N-Myc downstream-regulated gene 2 on EAAT1 expression was dependent on protein kinase B (Akt/PKB) rather than on NF-κB activity (Le et al., 2018). SLC1A3 expression can be altered by xenobiotics, and astrocytic SLC1A3 expression was associated with intraperitoneal injection of a synthetic Toll-like receptor (TLR)-3 ligand, polyinosinic acid, which also promoted IFN-β transcription in the CNS (Costello and Lynch, 2013). Moreover, dietary cocoa stimulated SLC1A3 expression while suppressing inflammatory cytokine expression during prolonged activation of trigeminal ganglion neurons and glia by complete Freund's adjuvant (Cady et al., 2013), whereas Acrolein, a neurotoxin produced in the brain during ischemic stroke, caused astrocytic inflammation via the NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome and downregulation of SLC1A3 (Park et al., 2020). Myelin-specific $CD4^+$ Th1 cells stimulated glutamate release by SLC7A11 in microglia, and SLC7A11 inhibition improved the conditions of EAE mice and decreased T cell infiltration into the CNS (Evonuk et al., 2015). Additionally, *Slc1a1*$^{+/-}$ mice have elevated levels of inflammatory cytokines in the brain (Afshari et al., 2017), and a *Slc1a1* suppressor microRNA (miR-26a) affected the response to IFN-β treatment in patients with MS (Potenza et al., 2018). Although peripheral nerve injury resulted in both upregulation of glucocorticoid receptors and downregulation of SLC1A1, inhibition of glucocorticoid receptors rescues SLC1A1 expression levels, possibly through the NF-κB signaling pathway (Wang et al., 2006). Furthermore, $1,25(OH)_2D_3$ regulates both *Slc1A1* and lipopolysaccharide (LPS)-binding protein CD14 in human osteoclasts (Tarroni et al., 2012).

Increased human endogenous retrovirus (HERV) gene activity occurs in immunologically activated glia, and HERV-W encoded glycoprotein syncytin is upregulated in glial cells within acute demyelinating lesions of MS patients (Antony et al., 2004). SLC1A4 was found to be a receptor of the HERV-W envelope protein syncytin-1, which could induce iNOS via old astrocyte specifically induced substance (OASIS), and OASIS suppressed astrocytic SLC1A4 (Antony et al., 2007). SLC1A5 was reported to be another syncytin-1 receptor and was highly expressed in human umbilical vein endothelial cells (Yan et al., 2017).

Syncytin-1 could be induced by TNF-α via the Wnt/*beta*-catenin pathway in squamous cell carcinoma cells 9, indicating that the interaction of SLC1A5-syncytin-1 may promote cancer-endothelial cell fusion (Yan et al., 2017).

SLC1A2 is also relevant to other nervous system disorders. The autoantibody neuromyelitis optica (NMO)-IgG, a biomarker of neuromyelitis optica, targets the aquaporin 4 water channel on astrocytes (Hinson et al., 2008). SLC1A2 expression levels vary according to changes in aquaporin 4 expression, suggesting that SLC1A2 might form complexes with aquaporin 4, and thus pathologically produced neuromyelitis optica (NMO)-IgG might cause excitotoxicity via aquaporin 4 binding (Hinson et al., 2008). Upregulation of SLC1A2 by an antibiotic, ceftriaxone, was shown to accompany downregulation of proinflammatory cytokines in rats with traumatic brain injury (Wei et al., 2012), and in amyotrophic lateral sclerosis, a stearyl-norleucine-vasoactive intestinal peptide rescued the levels and function of SLC1A2 via suppression of TNF-α and downregulation of NF-κB (Goursaud et al., 2015). SLC1A2 was also found to be reduced in brains of patients with Alzheimer's disease. SLC1A2 deprivation in astrocytes resulted in both innate and adaptive immune function failure, with gene expression pattern changes similar to those caused by inflammation and synaptic function changes in Alzheimer's disease or aged brains, which has been associated with early onset deficits in short-term memory; meanwhile, SLC1A2 deprivation in neurons was associated with late onset deficits in long-term memory (Sharma et al., 2019).

The SLC1A family also plays a key role in chronic pain, and arachidonic acid is a critical regulator of inflammatory pathways that increases pain sensitivity after nerve injury by activating inflammatory pathways and affecting microglia and astrocytes. The expression/activity of the glutamate transporter in the middle of the synaptic cleft leads to a sustained increase in the concentration of glutamate in and/or around the synaptic cleft, ultimately leading to the continued development of neuropathic pain (Gegelashvili and Bjerrum, 2019).

SLCs During Infection. Several studies suggested that SLC1A2 participates in viral infections, primarily in the CNS. Inflammatory macrophage activation during human immunodeficiency virus (HIV) infection caused CNS symptoms and was associated with glutamate excitotoxicity. However, macrophages were less affected by compensatory increased SLC1A2 expression and GS inhibition due to a reduction in glutamate transport during HIV replication, supporting a potential replacement of affected astrocytes (Porcheray et al., 2006). Astrocyte elevated gene-1 was found to promote HIV-1-associated neuroinflammation via suppression of SLC1A2 and the NF-κB pathway (Vartak-Sharma et al., 2014). During HIV-associated neurocognitive disorders, trace amine receptor 1 negatively regulated SLC1A2 expression and glutamate uptake, and trace amine receptor 1 disruption prevented the decrease in SLC1A2 mediated by methamphetamine, a trace amine receptor 1 agonist (Cisneros and Ghorpade, 2014). Japanese encephalitis virus infection in neurons caused astrogliosis, elevated SLC1A3 and SLC1A2 expression to detoxify glutamate, and induced other neuroprotective changes, which were nonetheless insufficient to overcome neuronal injuries (Mishra et al., 2007). In acute flaccid paralysis caused by the West Nile virus, the immune response to West Nile virus in the spinal cord influenced astrocytic glutamate reuptake, leading to higher extracellular glutamate and, thus, cells without direct virus infection were also damaged by excitotoxicity (Blakely et al., 2009). In the early stage of Borna disease virus infections, zebrin II/SLC1A6 expression was reported to be a marker for subsets of Purkinje cells with different susceptibility to the virus (Williams et al., 2007). SLC7A11 was identified as a receptor for Kaposi's sarcoma-associated herpesvirus, promoting cell fusion and virion entry of the virus (Kaleeba and Berger, 2006). In primary effusion lymphoma caused by Kaposi's sarcoma-associated herpesvirus, targeting SLC7A11 promoted apoptosis of primary effusion lymphoma cells, and inhibitors of SLC7A11 or downstream genes were potential therapeutic targets (Dai et al., 2015).

SLCs transporters have also been studied during bacterial infection. Inflammation in astrocytes could weaken gap junctions, and in the short term, hemichannel activity adjacent to Staphylococcus aureus-infected areas were directly correlated with an increased expression of connexin 43 (Cx43), Cx30, Pannexin 1 (Panx1), SLC1A3, and SLC1A2 (Karpuk et al., 2011). During *Helicobacter pylori* infection, *Slc7a2* knockout not only inhibited the innate immune response of mice, but also skewed the adaptive immune response from Th1 to Th2 (Barry et al., 2011). During Mycobacterium tuberculosis infection, avirulent strains led to higher SLC7A2 expression levels in macrophages than virulent strains, suggesting a role of SLC7A2 in controlling immune response of macrophages toward bacterial infection (Lee et al., 2019). Finally, proinflammatory signals and ***Slc7a5*** expression were both upregulated by *Shigella flexneri* infection in a new model of intestine named human intestinal enteroids (Koestler et al., 2019).

The impact of SLCs during parasitic and helminth infections is less known, but BALB/c mice, which are more susceptible to *Leishmania major* infection, showed higher *Slc7a2* expression in macrophages after IFN-γ or IL-4 treatment, and increased arginine might favor the growth of *Leishmania major* (Sans-Fons et al., 2013).

SLCs in Other Chronic or Autoimmune Diseases. SLCs have also been implicated in numerous other chronic inflammatory or autoimmunity diseases. Inflammatory bowel disease (IBD) mainly includes two distinct clinical conditions, Crohn's disease and ulcerative colitis (UC), and is thought to be caused by an abnormally activated immune response to normal luminal flora (Podolsky, 2002). Activating transcription factor 4 was downregulated in inflamed intestinal mucosa of patients with IBD, whereas *Slc1a5* transcription was suppressed by activating transcription factor 4 deficiency in mice, leading to lower glutamine uptake and antimicrobial peptide synthesis in intestinal epithelial cells (Hu et al., 2019). During active UC, tissue SLC7A2 and arginase-1 expression levels and arginine concentration were decreased, whereas NOS2, arginase-2 expression were higher (Coburn et al., 2016). Dextran sulfate sodium induced more severe UC in *Slc7a2* knockout mice. Similarly, in an azoxymethane-dextran sulfate sodium model of colitis-associated carcinogenesis, *Slc7a2* knockout resulted in increased proinflammatory cytokines/chemokines and decreased IL-4, C-X-C Motif Chemokine Ligand 9 (CXCL9), and CXCL10, skewing toward protumorigenic M2 activation of macrophages (Coburn et al., 2019). UC also reduced chromosome-associated protein D3 upregulating SLC7A5/CD98 expression, and system L or mTORC1 inhibition restored the bacterial clearance defects of colon epithelial cells lacking chromosome-associated protein D3 (Schuster et al., 2015).

Citrobacter rodentium is a widely used mouse model for human intestinal diseases including IBD. Arginine transporters are involved in conditions such as infections and IBD. In mice, *Slc7a2* expression is upregulated in colitis tissues after *Citrobacter rodentium* infection, and *Slc7a2* knockout weakened the immune response and attachment of *C. rodentium* to the epithelium (Singh et al., 2016). Another study showed that elevated arginine levels in the mouse colon at the peak of *C. rodentium* infection was correlated with downregulation of host *Slc7a2* and upregulation of *C. rodentium* virulence gene expression, indicating that the balance between host and pathogen was affected by arginine (Menezes-Garcia et al., 2020).

SLC1A3 and SLC1A2 are also enriched in the joints of the osteoarthritis rabbit model, resulting in higher concentrations of glutamate and aspartate (Hascup et al., 2016). In addition, in the rat retinal Müller cell line rMC-1 induced by high glucose, lower GS and SLC1A3 levels led

TABLE 2

Specific inhibitors associated with SLC1 and SLC7 transporters

Human Gene Name	Inhibitor	Formula	IC_{50}	Reference
SLC1A2	WAY-213613	$C_{16}H_{14}BrClF_2N_2O_4$	0.085 μM	(Simmons et al., 2014)
	DL-TBOA	$C_{11}H_{13}NO_5$	6 μM	(Pedraz-Cuesta et al., 2015)
	Dihydrokainic acid (DHK)	$C_{10}H_{17}NO_4$	23 μM(K_i)	(Arriza et al., 1994)
	T3MG	$C_6H_{11}NO_4$	90 μM	(Eliasof et al., 2001)
SLC1A3	UCPH-101	$C_{27}H_{22}N_2O_3$	0.66 μM	(Abrahamsen et al., 2013)
	UCPH-102	$C_{21}H_{18}N_2O_2$	0.42 μM	(Haym et al., 2016)
	DL-TBOA	$C_{11}H_{13}NO_5$	70 μM	(Shimamoto et al., 1998)
	WAY-213613	$C_{16}H_{13}BrF_2N_2O_4$	5 μM	(Hashimoto et al., 2018; Tao et al., 2020)
SLC1A5	Lobetyolin	$C_{20}H_{28}O_8$	N/A	(He et al., 2020)
	V-9302	$C_{34}H_{38}N_2O_4$	9.6 μM	(Schulte et al., 2018)
	GPNA hydrochloride	$C_{11}H_{14}ClN_3O_5$	55 μM(K_i)	(Corti et al., 2019)
SLC7A2	Platonin	N/A	N/A	(Chen et al., 2006)
SLC7A5	BCH	$C_8H_{13}NO_2$	131.5 μM	(Fraga et al., 2002; Kim et al., 2002)
	KMH-233	$C_{32}H_{25}N_7O_5$	18 μM	(Huttunen et al., 2016)
	GPNA hydrochloride	$C_{11}H_{14}ClN_3O_5$	250 μM.	(Corti et al., 2019)
	Lats-IN-1	$C_{18}H_{14}N_4OS$	0.51 μM (EC_{50})	(Kastan et al., 2021)
	JPH203	$C_{23}H_{19}Cl_2N_3O_4$	0.14 μM	(Oda et al., 2010)

GPNA, L-γ-Glutamyl-p-nitroanilide.

to higher glutamate levels, and higher IL-17A production and IL-17 receptor A, Glial Fibrillary Acidic Protein (GFAP), and vascular endothelial growth factor (VEGF) expression, indicating involvement of SLC1A3 in diabetic retinopathy, a complication of autoimmune diabetes (Qiu et al., 2017). During psoriasis, CD69 in skin gamma delta ($\gamma\delta$) T cells altered aryl hydrocarbon receptor-dependent IL-22 secretion and skin inflammation via its regulatory effect on surface expression of SLC7A5-CD98, L-tryptophan uptake, and tryptophan-derived aryl hydrocarbon receptor activators (Cibrian et al., 2016). Finally, in the murine lung during asthma, Arg1 deficiency improved the function and adaptive regulation of *Slc7a1* together with Arg2, Nos2, Slc7a7, Ccl2, Ccl11, Tnfα, and Ifnɤ, but failed to relieve airway inflammation (Zhu et al., 2021). *Slc7a1* expression was also upregulated in mammary alveolar epithelial cells by LPS stimulation in mouse mammary glands (Kobayashi et al., 2013).

SLC-Targeted Therapeutics and Conclusion. Over the past decades, a number of inhibitors targeting SLC1 and SLC7 transporters (Table 2) and many SLC-targeted therapeutics have been developed. However, for SLC1 and SLC7 family transporters only one Riluzole (SLC1A3) has been approved for the treatment of amyotrophic lateral sclerosis (Lin et al., 2015). Nonetheless, several preclinical studies suggest SLC-targeted therapeutics against cancer and MS. In breast tumors enriched with cancer stem cells, targeting SLC7A11 could stimulate immune response and improve chemotherapy sensitivity (Ruiu et al., 2019), leading to the development of a virus-like particle immunotherapeutic approach to target SLC7A11 protein (Bolli et al., 2017). Furthermore, SLC7A1 expression was enhanced in a arginine starvation model that mimics an important tumor immune evasion mechanism. Under arginine deprivation SLC7A1 inhibition resulted in arginine uptake and cellular proliferation blockade of T cells (Werner et al., 2016). In addition, since arginine synthesis was blocked and SLC7A1 was the only arginine transporter expressed in chronic lymphocytic leukemia cells, SLC7A1 inhibition may represent a promising chronic lymphocytic leukemia treatment (Werner et al., 2019). *Slc7a5* was also overexpressed in T cell malignancies, and its inhibitor JPH203 showed an antitumor effect (Rosilio et al., 2015).

Several agents have been proposed as potential MS therapies that rescue SLC1A3 and SLC1A2 expression. Matrine, a natural quinolizidine alkaloid, showed beneficial effects on inflammation and demyelination in EAE mice by lowering glutamate and increasing SLC1A3 and SLC1A2 expression and GABA concentrations in the brain (Kan et al., 2014). EAE mice treated with the immunosuppressive MS medication, fingolimod, exhibited less inflammation mediated by T cells and macrophages/microglia, less astrocyte activation, and restored SLC1A3, SLC1A2 levels in the inflamed spinal cord, potentially via an indirect mechanism (Lee et al., 2017). Similarly, In LPS-stimulated astrocytes, disruption of GluA2, a subunit of glutamate receptor α-amino-3-hydroxy-5-methyl-4-isox-azolepropionic acid receptor (AMPAR), by an interfering peptide rescued the expression levels of SLC1A3, SLC1A2, and relieved the MS symptoms of EAE mice (Lee et al., 2018). Besides matrine and fingolimod, we found three agonists of SLC1A2. The first one is LDN-212320, which can increase the level of SLC1A2 protein in astrocytes (Xing et al., 2011); the second is GPI-1046, which is an antibiotic-free immunoavidin ligand that reduces ethanol intake by upregulating SLC1A2 in the prefrontal cortex (PFC) and nucleus accumbens (NAc) cores (Sari and Sreemantula, 2012); the last one is GT 949, which enhances glutamate transport with an EC_{50} of 0.26 ± 0.03 nM. GT 949 also demonstrates selectivity to SLC1A2 and has no effect on glutamate activity mediated by SLC1A3 or SLC1A1 (Kortagere et al., 2018).

In patients with obesity, a population of T cells called mucosal-associated invariant T cells were dysregulated and showed defective glycolytic metabolism and amino acid transport by SLC7A5 necessary for downstream mTORC1 signaling (O'Brien et al., 2019). SLC7A5 inhibition controlled the proliferation of gamma delta ($\gamma\delta$) T cells, IL-17 secretion of $CD4^+$ T cells, and the inflammatory response of both cells via the IL-23 and IL-1β-induced PI3K/protein kinase B (AKT/PKB)/mTOR pathway in psoriasis (Cibrian et al., 2020). For neurologic disease, astrocytes have high transport capacity and affinity for the SLC7A5 substrate [14C]-L-leucine, followed by neurons and microglia; hence, such prodrug can use Lat1 for cellular uptake with much higher activity than one of its parent drugs (Huttunen et al., 2019).

Currently, there are no reports on the gene single nucleotide polymorphisms (SNPS) of SLC1 and SLC7 family members directly in inflammatory and autoimmune diseases. The diseases related to SLC1 family single nucleotide polymorphisms (SNPs) were mainly obsessive-compulsive disorder, schizophrenia, epilepsy, essential tremor, stress depression, and multiple system atrophy (Soma et al., 2008; Wendland et al., 2009; Gadow et al., 2010; Jiménez-Jiménez et al., 2015; Ritter et al., 2016; Yu et al., 2018; Ghosh et al., 2020). The SLC7 family is mostly associated with susceptibility to leprosy, multiple myeloma,

schizophrenia, and tuberculosis (Cai et al., 2018; Wang et al., 2018, 2020b; Poi et al., 2019).

Taken together, SLCs of amino acids, especially SLC1 family members as glutamate transporters and SLC7 members as arginine transporters, play important roles in various conditions involving inflammation and immune responses, such as MS, IBD, viral infections, tumor immunotherapies, and chronic intestinal inflammation via modulating the function of astrocytes, macrophages, and T cells. Further studies should focus on determining the specific mechanism of these SLCs in regulating immune functions and course of diseases, developing specific inhibitors as potential therapy for these diseases or characterizing the numerous SLCs that still remain to be studied.

Authorship Contributions

Participated in research design: Chen.
Performed data analysis: Sheng, Luo.
Wrote or contributed to the writing of the manuscript: Sheng, Luo, Chen.

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