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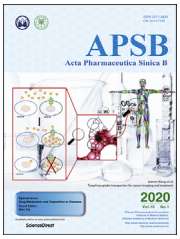

REVIEW

Solute carrier transporters: the metabolic gatekeepers of immune cells

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KEY WORDS

Solute carrier;
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Abstract Solute carrier (SLC) transporters meditate many essential physiological functions, including nutrient uptake, ion influx/efflux, and waste disposal. In its protective role against tumors and infections, the mammalian immune system coordinates complex signals to support the proliferation, differentiation, and effector function of individual cell subsets. Recent research in this area has yielded surprising

Abbreviations: 3-PG, 3-phosphoglyceric acid; ABC, ATP-binding cassette; AIF, apoptosis-inducing factor; α-KG, α-ketoglutaric acid; AP-1, activator protein 1; ASCT2, alanine serine and cysteine transporter system 2; ATP, adenosine triphosphate; BCR, B cell receptor; BMDMs, bone marrow-derived macrophages; CD45R, a receptor-type protein tyrosine phosphatase; CTL, cytotoxic T lymphocytes; DC, dendritic cells; EAATs, excitatory amino acid transporters; ER, endoplasmic reticulum; ERRα, estrogen related receptor alpha; FFA, free fatty acids; G-6-P, glucose 6-phosphate; GLUT, glucose transporters; GSH, glutathione; HIF-1α, hypoxia-inducible factor 1-alpha; HIV-1, human immunodeficiency virus type 1; Hk1, hexokinase-1; IFNβ, interferon beta; IFNγ, interferon gamma; IKK, IκB kinase; IKKβ, IκB kinase beta subunit; IL, interleukin; iNOS, inducible nitric oxide synthase; iTregs, induced regulatory T cells; LDHA, lactate dehydrogenase A; LPS, lipopolysaccharide; Lyn, tyrosine-protein kinase; MAPK, mitogen-activated protein kinase; MCT, monocarboxylate transporters; MS, multiple sclerosis; mTORC1, mammalian target of rapamycin complex 1; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; NOD2, nucleotide-binding oligomerization domain containing 2; PEG2, prostaglandin E2; Pfk, phosphofructokinase; PI-3K/AKT, phosphatidylinositol-3-OH kinase/serine–threonine kinase; PPP, pentose phosphate pathway; RA, rheumatoid arthritis; RLR, RIG-I-like receptor; ROS, reactive oxygen species; SLC, solute carrier; SLE, systemic lupus erythematosus; SNAT, sodium-coupled neutral amino acid transporters; STAT, signal transducers and activators of transcription; TAMs, tumor-associated macrophages; TCR, T cell receptor; TCA, tricarboxylic acid; Teffs, effector T cells; Th1/2/17, type 1/2/17 helper T cells; TLR, toll-like receptor; TNF, tumor necrosis factor; Tregs, regulatory T cells; TRPM7, transient receptor potential cation channel subfamily M member 7; VEGF, vascular endothelial growth factor; ZIP, zrt/irt-like proteins.

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Glucose;
Glutamine;
Metal ion

findings on the roles of solute carrier transporters, which were discovered to regulate lymphocyte signaling and control their differentiation, function, and fate by modulating diverse metabolic pathways and balanced levels of different metabolites. In this review, we present current information mainly on glucose transporters, amino-acid transporters, and metal ion transporters, which are critically important for mediating immune cell homeostasis in many different pathological conditions.

1. Introduction

Transporters are specialized proteins that translocate substrates across cellular membranes. They are usually classified as influx and efflux transporters. Influx transporters facilitate the entry of substrates into the cytoplasm, while efflux transporters are responsible for the movement of molecules out of the cell[1]. Typically, uptake of substrates is primarily carried out by transporters from the solute carrier (SLC) family, which do not depend directly on adenosine triphosphate (ATP) hydrolysis[2–4]. By contrast, efflux occurs against a substrate concentration gradient and is usually mediated by transporters from the ATP-binding cassette (ABC) family that rely on ATP hydrolysis[5,6]. Nonetheless, some SLC transporters function as bidirectional or even efflux transporters.

SLC transporters-the largest transporter family consisting of 456 integral membrane proteins[7] that facilitate the import and export of a wide array of small molecules across biological membranes-control essential physiological functions ranging from nutrient uptake to drug absorption and disposition[8]. SLC transporters are facilitated or secondary active transporters that translocate soluble molecules across cellular membranes. They facilitate the passive diffusion of specific small molecules, function as exchangers, or utilize ion gradients to drive flow against gradients[9].

SLC transporters are widely present and abundant in the body. They act as a barrier in protective organs such as the intestines and placenta, and are also ubiquitous in major metabolic organs, such as the liver[10,11], kidneys[12], or even present in endocrine organs like adipose tissues[13]. Additionally, there is increasing evidence show that various types of immune cells express individual SLC transporters, and these transporters may affect cellular decisions, including development, homeostasis, and activation/differentiation[14].

The immune system is crucial for the defense against pathogen-induced infection and diseases, which comprises specialized cell populations experiencing adaptive and dynamic metabolic changes throughout their lifespan[15]. Therefore, immune cells are excellent models to study the functional outcomes of cellular metabolism[16], and according to an emerging perspective, their differentiation and even function can be regulated by cellular metabolism, consequently influencing the adaptive and innate immune response[17]. Generally, the immune cells can be roughly divided into lymphoid and myeloid lineages[18].

Macrophages, key representative of myeloid lineages, represent an innate immune cell forming the first barrier that protects against invading pathogens[19]. Two polarized types of macrophages have been recognized, named the classically activated (or M1) macrophages and the alternative activated (or M2) macrophages[20]. Exposure to Toll-like receptor (TLR) ligand, with or without interferon-γ (IFNγ), polarizes macrophages into the proinflammatory state, M1 phenotype, which is featured by the expression of proinflammatory cytokines, inducible nitric oxide synthase (iNOS or NOS2), and strong microbicidal activity[20]. In contrast, prototypical type 2 T-helper (Th2) cytokines (IL-4 and IL-13)-stimulated macrophages (M2 phenotype) is associated with tissue remodeling and resolution of the inflammation[20]. Actually macrophages have high plasticity and can switch between these two activated states through dynamic processes. A new nomenclature linked to the activation standards has been proposed to describe the polarized macrophages generated by the stimulation of different mediators[21].

For another, T and B cells are two most vital components of lymphocyte lineages for the adaptive immune system[22,23]. T or B cell deficiencies are shown to lead to severe immunodeficiencies[24]. As such, the different stages of T cells are integrated with systemic inflammation and conducive to protecting the host from invading pathogens[25]. T cells are divided into two functionally distinct lineages by the exclusive expression of the co-receptor CD4 or CD8[26]. In response to cognate antigens, naïve $CD4^+$ T cells differentiate into T helper cells (Th1, Th2, and Th17), effector T cells (Teffs), and immunosuppressive regulatory T cells (Tregs)[27]. Likewise, naïve $CD8^+$ T cells proliferate and differentiate into cytotoxic effector cells to eliminate infected or malignant cells upon cognate antigen stimulation[27]. And only a small portion of them eventually forms the memory population after rapid expansion and concomitant contraction[28]. Specifically, B cells are responsible for mediating the humoral arm of the adaptive immune system, and perform as a central contributor in the pathogenesis of immune system involving antibodies production[29].

During the immune response, immune cells alter their metabolic activities. Although most research on the regulation of immune responses has focused on signal pathways, emerging data suggests that cellular metabolism is also a principal modulator of immune cell proliferation, differentiation, and activation[30–33]. Activated immune cells dramatically increase their nutrient uptake and metabolism, relying on numerous transporters to support the energetic needs for effector function. This process has a profound impact on some forms of cancer and autoimmune diseases, with implications for future therapeutic strategies[34]. The cellular uptake and utilization of nutrients or minerals such as iron, which is mediated by SLC transporters, highly affects the development, homeostasis, activation, and differentiation of immune cells.

In this review, we concentrate on the following five aspects, which we believe to offer exciting current and future research directions: (a) glucose transporters in immune-cell metabolism, focusing on T cells and macrophages; (b) glutamine transporters

in T cell metabolism; (c) glutamate transporters in macrophages; (d) lactate transporters in T cells and macrophages; (e) functions of metal-ion SLC transporters in immune cells growth, differentiation, and immune responses; (f) other transporters whose substrates are indispensable during the inflammatory responses especially in the defense against various pathogens.

2. Glucose transporters in immune-cell metabolism

2.1. *T-cell metabolism*

In the resting state, naïve and memory T cells have relatively low energy needs, but once activated, T cells initiates a rapid transition to a highly metabolically active state, dramatically increasing their energetic and biosynthetic requirements to support growth, differentiation, proliferation, and effector function[35]. The "Warburg effect", which was firstly used to describe the phenomenon that cancer cells mainly rely on enhanced glucose uptake and aerobic glycolysis to survive[36], is also a key factor in maintaining the activation and differentiation of T cells.

The facilitative glucose transporter family supports the increased glucose uptake of T cells during activation, which provides a key control point in the T-cell-specific Warburg effect. In humans, the glucose transporter family consists of 14 members, known as glucose transporters (GLUT) or solute carrier 2A (SLC2A) 1 to 14, many of which possess distinct subcellular localizations, substrate specificities, and transport kinetics[37]. The dynamic functions of GLUT transporters in the activation and differentiation of T cells have not yet been clearly defined.

GLUT1 is the primary glucose transporter of lymphocytes, where it acts as an important regulatory nexus during T cell activation, and its relative cell-surface expression defines thymocyte differentiation[38], as well as the identification of $CD4^+$ and $CD8^+$ T-cell subsets[39], memory T cells[31], and Tregs[40,41]. Under physiological glucose concentrations, the GLUT1 transporters of T lymphocytes are usually saturated. As a result, glucose import *via* GLUT1 is regarded as the rate-limiting step in the glucose metabolism of T cells.

In quiescent T cells, the cell surface expression of GLUT1 is nearly undetectable[31], but upon activation, GLUT1 is immediately trafficked to the cell membrane and mediates glucose influx to accommodate the dramatic increase of metabolic demands[35,42,43] (Fig. 1).

Although it has been shown that activated $CD4^+$ T cells and cytotoxic $CD8^+$ T cells share similar metabolic preferences, new data indicate that there are important differences in their metabolic adaptations. The surface abundance of GLUT1 in $CD4^+$ and $CD8^+$ T cells is drastically increased following T cell receptor (TCR) activation *in vitro*[16,31,39] and infection with HIV-1 *in vivo*[44]. Interestingly, abolishing GLUT1 selectively limits the activation and effector function of $CD4^+$ but not $CD8^+$ T cells, which indicates a potential role of other glucose transporters in the metabolic reprogramming of $CD8^+$ T cells[45]. A more recent study demonstrated that activated $CD4^+$ T cells primarily rely on glucose as their oxidative fuel, while $CD8^+$ T cells have higher glycolytic flux and exhibit more metabolic flexibility in glucose-starved environments[46].

The differentiation of $CD4^+$ T cells is now recognized as dynamic, and proinflammatory $CD4^+$ T cells are able to redifferentiate into Th1, Th2, or Th17 subsets in response to environmental stimuli, while the anti-inflammatory subset is referred to as induced regulatory T cells (iTregs)[47]. Importantly, distinct T cell subsets bear different metabolic signatures.

Th1 cells produce IFNγ and tumor necrosis factor (TNF), and mediate responses to intracellular pathogens and bacteria. Th2 cells are active in the regulation of immune responses to helminths. Th17 cells are important for the defense against extracellular fungi and bacteria[48]. Moreover, Tregs induce immune tolerance against allo-antigens and self-antigens[49].

Compared with Tregs, Th1, Th2, and Th17 cells differentiated *in vitro* under IL-2 stimulation possess higher total cellular and cell-surface expression levels of GLUT1. Tregs, in contrast, have low GLUT1 expression levels and high rates of fatty acid and pyruvate oxidation *in vitro*[41,50–52]. Glucose metabolism also controls choices in the T cell lineage. Transgenic expression of GLUT1 promotes T cell activation, improves the function of Teffs, and leads to the generation of readily activated memory-phenotype-like T cells, with possible immunopathological effects in aged mice[31]. Furthermore, it also drives $CD8^+$ T cells towards a terminally differentiated and more short-lived state. GLUT1 overexpression can also promote the incidence of inflammatory diseases[31]. Genetic deletion of GLUT1 indicated that $CD4^+$ Teffs (Th1, Th2, and Th17 cells) rely on this glucose transporter for their expansion and survival, while Tregs appear to be primarily GLUT1-independent. These data are consistent with the theory of preferential glycolysis in Teffs and mitochondrial oxidation in Tregs described by Michalek et al.[51].

The protein synthesis inhibitor cycloheximide did not prevent the return of GLUT1 to the cytoplasm, indicating that trafficking of GLUT1 relies on recycling from intracellular stores and is not immediately dependent on *de novo* protein synthesis[53]. When cytokines were withdrawn from hematopoietic cell lines, GLUT1 was internalized and returned back to the cell membrane upon renewed addition of IL-3[53]. The phosphatidylinositol-3-OH kinase/serine-threonine kinase (PI-3K/AKT) pathway plays a vital role in IL3-induced GLUT1 trafficking[53]. Furthermore, pharmacological inhibition of PI-3K activity led to decreased GLUT1 cell-surface levels mediated by IL-3, while constitutive overexpression of AKT can maintain the surface-localization of GLUT1 without IL-3[53]. In addition, the metabolic checkpoint kinase complex mTORC1[53], cMYC[54], and estrogen related receptor alpha (ERRα)[55] transcription factors also increase the expression of GLUT1 and downstream aerobic glycolysis in T cells to support their proliferation and effector function.

Recently, there have been reports that glucose transporters other than GLUT1 may have the potential to support the metabolic needs of activated T cells. GLUT3, GLUT4, and GLUT6 as well as GLUT1 show activation-dependent mRNA upregulation in human $CD4^+$ T cells, and are further enhanced when the cells are infected with HIV-1[56]. Studies also suggested an indispensable role of GLUT3-mediated glucose uptake in the GLUT1-independence of $CD8^+$ Teffs and resting T cells in view of their high expression of GLUT3 in addition to GLUT1[45] (Fig. 1). However, the specific functions of these glucose transporters in different immune-cell subtypes and inflammatory processes still need to be elucidated.

2.2. *Macrophage metabolism*

The canonical M1 and M2 activated macrophages show distinct regulation patterns in their glucose metabolism. M1 polarized macrophages (in response to IFNγ or TLR ligands) display a major dependence on glycolysis[30,57,58], while M2 polarized ones

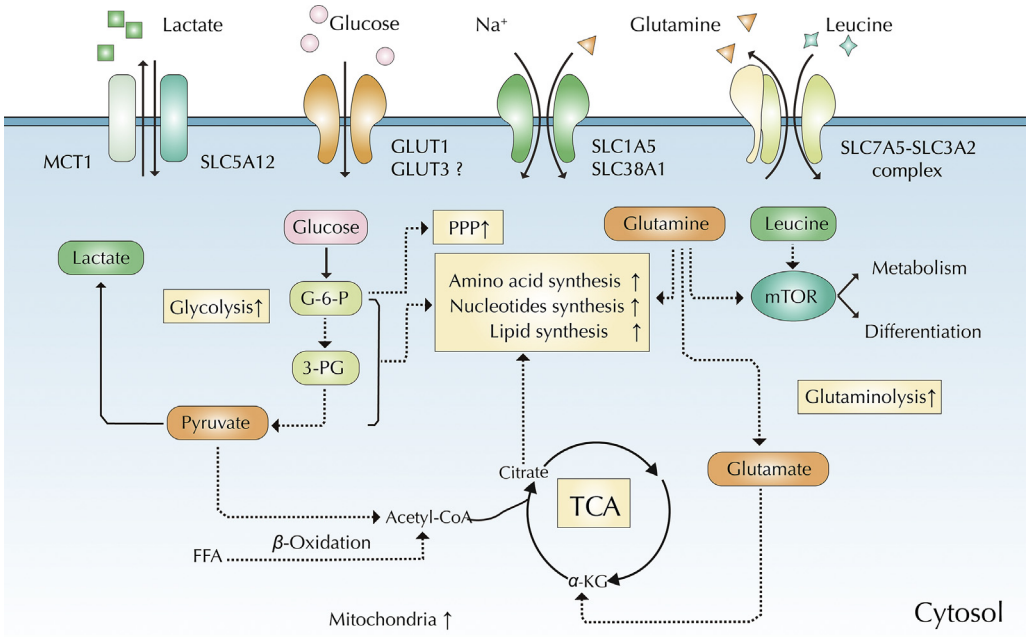

Figure 1 T cell activation leads to increased uptake of glucose and glutamine uptake as well as lactate secretion. GLUT1 and GLUT3 mediate increased glucose uptake, which enhances aerobic glycolysis to sustain T-cell activation and promote their differentiation. To maintain high glycolytic activity and ATP production, the conversion of NAD^+ to NADH must be reversed rapidly. To accomplish this, activated T cells convert the glycolytic end product pyruvate into lactate. Under high extracellular lactate concentrations, $CD4^+$ and $CD8^+$ T cell subsets internalize lactate through SLC15A2 and MCT1 (SLC16A1), respectively, upon entering inflammatory sites. SLC1A5 or SLC38A1 cotransport polarized Na^+ and glutamine, while concentrated glutamine is exchanged for leucine by the SLC7A5-SLC3A2 complex, which is also known as CD98. Leucine and glutamine promote the activation of mTORC1 through direct and indirect mechanisms, which regulates T cell metabolism and cell differentiation of the Th1 and Th17 subsets. MCT, monocarboxylate transporter; SLC, solute carrier transporter; GLUT, glucose transporter; PPP, pentose phosphate path; G-6-P, glucose 6-phosphate; 3-PG, 3-phosphoglyceric acid; mTOR, the target of rapamycin; FFA, free fatty acids; α-KG, α-ketoglutaric acid; TCA cycle, tricarboxylic acid cycle.

(in response to IL-4 and IL-13), mainly rely on mitochondrial oxidative metabolism[58–61], with a lesser dependence on the anaerobic glycolytic pathway[62].

It has been previously reported that GLUT1 is a critical regulator of glucose metabolism in macrophages[30]. When GLUT1 was overexpressed in macrophages, the glucose uptake and the expression of proinflammatory cytokines (TNF-α, IL-1b, and IL-6) were significantly increased even without activation by specific stimuli. In addition, GLUT1-deleted bone marrow-derived macrophages (BMDMs) displayed a reduced inflammatory phenotype and oxidative stress, along with increased levels of metabolites indicative of alternative activation (ornithine and polyamines)[63]. Interestingly, although the removal of GLUT1 limits glycolysis and the pentose phosphate pathway (PPP) in diet-induced obese mice, macrophages are metabolically flexible enough that this impairment leads to only subtle defects due to compensation through the metabolism of other substrates[63].

GLUT6 (SLC2A6, previously known as GLUT9) is another transporter belonging to the GLUT family, and its mRNA expression is upregulated in macrophages after lipopolysaccharide (LPS) stimulation[64]. Although metabolomics and *in vitro* analyses indicates that GLUT6 has the potential to modulate the glycolysis pathway in inflammatory macrophages, $GLUT6^{-/-}$ mice exhibited only a subtly different response to LPS administration compared with $GLUT^{+/+}$ ones[64]. While GLUT6 was previously reported to mediate glucose uptake in endometrial cancer cells[65], at least in macrophages, the lysosomally located GLUT6 is not a true glucose transporter, and its physiological roles in immune cells still need to be clarified further[64]. The information reviewed above glucose transporters involved in immune cells are summarized in Table 1[66–86,87-119].

3. Glutamine transporters in T-cell metabolism

Glutamine is one of the most abundant amino acids in circulation. In addition to glucose metabolism, T cells utilize glutaminolysis to meet their dramatic energetic and biosynthetic demands[120]. Glutamine is converted to glutamate by deamination and glutamate is then transformed to α-ketoglutarate, which may feed into other metabolic pathways like the tricarboxylic acid (TCA) cycle and lipid synthesis[226].

The expression of glutamine transporters and glutaminolysis components is increased in activated T cells through a MYC-dependent pathway[121]. Compared with unstimulated T cells, activated T cells have 5−10 times higher glutamine uptake rates, and glutamine starvation impairs the late events of activation, such as cell proliferation and cytokine secretion, although it has no effect on the initiation of the activation and expression of T-cell surface markers. Several amino acid transporters were identified as crucial mediators of glutamine uptake in T cells. The *SLC38* (sodium-coupled neutral amino acid transporters, SNAT) gene family contains transporters that mediate the entry of glutamine into cells[122], and activation of T cells with CD3 and CD28 induces SLC38A1 and SLC38A2 expression levels, enhancing their relocation from intracellular vesicles to the cell surface[123].

Table 1 Properties and functions of glucose, glutamine, and lactate transporters in immunometabolism.

Gene	Alias	Transport mechanism	Substrate	Inhibitor/blocker	Comment	Polymorphism	Ref.
SLC2A1	*GLUT1*	Facilitated transporter, high affinity for glucose	Glucose (K_m = 3 mmol/L), galactose (K_m = 17 mmol/L), mannose (K_m = 20 mmol/L), glucosamine (K_m = 2.5 mmol/L), DHA (K_m = 1.1 mmol/L)	Apigenin, fasentin (IC_{50} = ~68 μmol/L), oxime derivatives (IC_{50} = ~9–24 μmol/L), EF24, WZB27 (IC_{50} = ~5 μmol/L), WZB115 (IC_{50} = ~0.3 μmol/L), WZB117 (IC_{50} = ~10 μmol/L), BAY 876 (IC_{50} = ~2 nmol/L), STF 31 (IC_{50} = ~1 μmol/L)	• GLUT1 is nearly undetectable in quiescent T cells. • Increased surface abundance of GLUT1is observed in $CD4^+$ and $CD8^+$ T cells following TCR or infected with HIV-1. • CD4 Teffs but not Tregs rely on GLUT1 for their expansion and survival. • Transgenic expression of Glut1 augments T cell activation. • GLUT1 deleted BMDMs display a reduced inflammatory phenotype and oxidative stress.	Rs1385129 in *SLC2A1* is linked to poor $CD4^+$ T Cell recovery in antiretroviral-treated HIV^+ individuals.	66–72
SLC2A3	*GLUT3*	Facilitated transporter, high affinity for glucose	Glucose (K_m = 1.4 mmol/L), galactose (K_m = 8.5 mmol/L), mannose, xylose, DHA	Glycogen synthase kinase-3β inhibitors, adriamycin, camptothecin, BAY 876 (IC_{50} = ~1.67 μmol/L), WZB117, cytochalasin B (K_i = ~0.4 μmol/L), phloretin, phlorizin	• GLUT3 has the potential to mediate GLUT1-independence glucose uptake in $CD8^+$ Teffs and resting T cells.	A 129-kb deletion related to *SLC2A3* confers substantial protection against rheumatoid arthritis.	73–76
SLC2A4	*GLUT4*	Facilitated transporter, insulin-responsive transporter	Glucose (K_m = 5 mmol/L), DHA (K_m = 0.98 mmol/L), glucosamine (K_m = 3.9 mmol/L)	Fasentin (IC_5 = ~68 μmol/L), BAY 876 (IC_{50} = ~0.29 μmol/L), WZB117, cytochalasin B (IC_{50} = ~0.2 μmol/L), phloretin (IC_{50} = ~10 μmol/L), phlorizin (IC_{50} = ~140 μmol/L)	• GLUT4 shows activation-dependent mRNA upregulation in human $CD4^+$ T cells.	–	77,78
SLC2A6	*GLUT6* (originally named *GLUT9*)	Facilitated transporter, low affinity for glucose	Glucose	–	• GLUT6 shows activation-dependent mRNA upregulation in human $CD4^+$ T cells.	–	79
SLC38A1	*ATA1, GInT, NAT2, SA2, SAT1*	Sodium-coupled transporter, highly temperature dependent transporter	Glutamine (K_m = 0.3 mmol/L), alanine (K_m = 0.3 mmol/L), asparagine, cysteine,	Amino acid analog *N*-methylaminoisobutyric acid (MeAIB), L-theanine	• Activation of T cells with CD3 and CD28 induces SLC38A1 expression levels.	–	80–85

(*continued on next page*)

Table 1 (*continued*)

Gene	Alias	Transport mechanism	Substrate	Inhibitor/blocker	Comment	Polymorphism	Ref.
			histidine, serine				
SLC38A2	*ATA2, KIAA1382, SA1, SAT2*	Sodium-coupled transporter, pH-sensitive transporter	Alanine, asparagine, cysteine, glutamine, glycine, histidine, methionine, proline, serine	*N*-Methyl-D-glucamine, choline, 2-methylamino-isobutyric acid (K_m = ~0.39 mmol/L, pH 8.0)	• Activation of T cells with CD3 and CD28 induces SLC38A2 expression levels.	–	86,87
SLC1A5	*ASCT2, M7V1, RDR, RDRC*	Sodium-coupled transporter	Alanine, serine, cysteine, threonine, cysteine	Benzylserine, γ-Glu-*p*-nitroanilide (IC_{50} = ~1000 μmol/L), 1,2,3-dithiazoles (IC_{50} = ~3–30 μmol/L), 2-substituted *N*γ-glutamylanilide (IC_{50} = ~1.3 μmol/L), V-9302 (IC_{50} = ~9.6 μmol/L)	• Rapid uptake of glutamine through SLC1A5 is triggered in TCR-stimulated naïive $CD4^+$ T cells. • SLC1A5 is required Th1 and Th17 cells induction, inflammatory T cell responses, and T cell receptor (TCR)-stimulated activation of the metabolic kinase mTORC1. • SLC1A5 is a major regulator of glutamine transport in T lymphocytes.	Polymorphisms in *SLC1A5* and *SLC7A5* influence *ex vivo* cytokine responses to *M. tuberculosis*, especially for T-cell cytokines.	88–96
SLC16A1	*MCT1, MOT1*	Proton-coupled monocarboxylate transporter	Lactate, pyruvate, ketone bodies	2-Cyano-3 (4-hydroxyphenyl)-2-propenoic acid (CHC), 4,4′-di-isothiocyanostilbene-2,2′-disulfonate (DIDS), 4,4′-dibenzamidostilbene-2,2′-disulfonate (DBDS), AR-C177977, AR-C122982, AR-C155858, AZD3965, acriflavine, pcuribenzene sulfonate	• MCT1 internalizes lactate in human cytotoxic T lymphocytes (CTL) under high lactate condition.	rs1049434 in *SLC16A1*, exhibits increased lactate transport *via* SLA16A1 compared to the wild type Asp/A, seems to be is correlated with better multiple myeloma patient's survival.	97–101
SLC16A3	*MCT4*	Proton-coupled monocarboxylate transporter	Lactate, ketone bodies	2-Cyano-3-(4-hydroxyphenyl)-2-propenoic acid (CHC), 4,4′-di-isothiocyanostilbene-2,2′-disulfonate (DIDS), 4,4′-dibenzamidostilbene-2,2′-disulfonate (DBDS), acriflavine	MCT4 is required for macrophage activation by TLR2 and TLR4 agonists, and helps sustaining high glycolysis and expression of proinflammatory mediators.	–	97–99
SLC5A12	*SMCT2*	Sodium-coupled transporter	Lactate, pyruvate, nicotinate, propionate, butyrate and beta-D-hydroxybutyrate	Ibuprofen (IC_{50} = 64 μmol/L), fenoprofen (IC_{50} = 119 μmol/L), ketoprofen (IC_{50} = 27 μmol/L)	SLC5A12 senses high lactate concentrations upon entering inflammatory sites in $CD4^+$ T cell subsets.	–	102
SLC1A2	*EAAT2, GLT1*	X_{AG}^-, sodium- and potassium-dependent	L-Glutamate (K_m = 391 μmol/L), L- and D-aspartate	WAY213613	X_{AG}^- regulates intracellular GSH store in monocyte-derived macrophages.	–	103–109

SLC1A3	*EAAT1, GLAST-1, EA6*	transporter X_{AG}^-, sodium-dependent transporter	L-Glutamate (K_m = 525 μmol/L), L- and D-aspartate	UCPH101	X_{AG}^- regulates intracellular GSH store in monocyte-derived macrophages.	–	103,107–112
SLC7A11	*CCBR1, xCT,*	Xc^-, sodium-independent, anionic amino acid transport system	Cystine, glutamate (preferentially extracellular cystine against intracellular glutamate)	Erastin (IC_{50} = 0.14 μmol/L in Calu-1, IC_{50} = 0.20 μmol/L in HT-1080), sulfasalazine (IC_{50} = 460 μmol/L in Calu-1, IC_{50} = 450 μmol/L in HT-1080), sorafenib, aminoadipate	SLC7A11 regulates intracellular GSH store in mouse macrophage and mediates macrophage-induced glutamate-dependent neurotoxicity.	–	113–119

–Not applicable.

In addition, the SLC1A5 (alanine serine and cysteine transporter system 2, ASCT2)[124], is also an important glutamine transporter whose expression levels are upregulated upon T cell activation[125]. It was recently demonstrated that rapid uptake of glutamine through SLC1A5 is triggered in TCR-stimulated naïve $CD4^+$ T cells. Furthermore, SLC1A5 was identified as necessary for coupling the TCR and CD28 signals to activate mTORC1 pathway. Although SLC1A5 was revealed to be particularly important for the differentiation of Th1 and Th17 cells, it remains unclear which glutamine transporters meditate the initial T cell activation, including proliferation and IL-2 induction (Fig. 1). The information reviewed above glutamine transporters involved in immune cells are summarized in Table 1.

4. Glutamate transporters in macrophages

Despite the undoubted importance of glutamine metabolism in immune systems, relatively little is known about the function of glutamine transporters in macrophages. However, accumulating evidence suggests that glutamate transporters may play a role in mediating the immune functions of macrophages.

Due to the indispensable roles of glutamate as a neurotransmitter in the central nervous system, extracellular glutamate concentrations are tightly regulated by glutamate transporters[126]. Several glutamate transport systems have been identified. The first one is the family of excitatory amino acid transporters (EAATs), which were firstly identified in astrocytes (EAAT-1 and EAAT-2) and neurons (EAAT-3, EAAT-4, and EAAT-5)[127,128], removing glutamate from extracellular space[129,130]. The inward transport of one L-glutamate molecule by EAATs is coupled with inward uptake of three Na^+ and one H^+ ion, and outward movement of one K^+ ion[129,131]. The second system Xc^- is composed of xCT (SLC7A11) and 4F2 heavy chain (4F2hc). It is a Na^+-independent transport system for anionic amino acids, with high specificity for L-glutamate and L-cystine. Xc^- was first reported in mouse peritoneal macrophages cultured *in vitro* and can be strongly induced by bacterial LPS or reactive oxygen species (ROS)-generating agents[116,117]. It is a major way to provide cystine for glutathione and protein synthesis[132–134]. The third system X_{AG} is also Na^+-independent and demonstrates an affinity for glutamine, cystine, and aspartate[135,136].

Commonly, in exchange for intracellular glutamate, cystine is taken up into cells and then reduced to cysteine, which is vital for maintaining glutathione (GSH) levels[116,134]. In human monocyte-derived macrophages, Xc^- and X_{AG} systems are responsible for glutamate uptake[108]. Extracellular glutamate increases intracellular GSH synthesis in these macrophages, suggesting that glutamate transporters may be involved in GSH synthesis regulation of macrophages[109]. GSH synthesized from glutamate, cysteine, and glycine, is particularly important for immune cells in maintaining thiol redox state and protecting from oxidative stress[137].

5. Lactate transporters in immunometabolism

Although lactate was previously believed to be only a dead-end waste product of glycolysis, substantial evidence highlighted its critical role not only in regulating tumor immune surveillance but also in the regulation of immune function[138–140].

Lactic acid is transported across biological membranes through four reversible monocarboxylate transporters (MCT) (lactate–H^+ symporter) that belong to the SLC16 family of solute carriers comprising a total 14 members that share highly

conserved characteristic motifs[141]. The transport direction of MCTs is determined by the concentration gradients of both monocarboxylate ions and protons. There is evidence that different MCTs facilitate lactic acid transport between cells. The most ubiquitously expressed family member, MCT1, facilitates lactate and pyruvate exchange and is induced by c-MYC[142]. Very similar to MCT1 but less expressed in human tissues, MCT2 displays a higher affinity for L-lactic acid and pyruvate. By contrast, MCT3 and MCT4 share similar functions and are efficient lactate exporters, fulfilling a key function in glycolytic cells and the retinal pigment epithelium[141]. Similarly, sodium-coupled lactate transport is also performed by the widely expressed high-affinity transporter SLC5A8 or the low-affinity transporter SLC5A12[143].

The physiological concentration of lactate in normal tissues is about 1.5−3 mmol/L[143], but can increase to 10−12 mmol/L at sites of inflammation such as atherosclerotic plaques or rheumatic synovial fluid, and even rise up to 20−30 mmol/L in tumors[139,144,145].

Under high extracellular lactate concentrations, human cytotoxic T lymphocytes (CTL) were demonstrated to internalize lactate through MCT1[146,147]. It was later reported that $CD4^+$ and $CD8^+$ T cell subsets sense high lactate concentrations upon entering inflammatory sites *via* SLC5A12 and MCT1, respectively, and detrimentally undergo T cell motility inhibition, produce higher amounts of IL-17 and lose cytolytic activity due to interference with glycolysis *via* inhibition of phosphofructokinase (PFK) or downregulation of hexokinase-1 (HK1)[144,148] (Fig. 1). Notably, these effects on T cell migration were not only observed in *in vitro* experiments, but also in a peritonitis model[144]. Although lactate can generally inhibit the activity of effector T cells, it has limited effects on the function of Tregs[149].

Crucially, Zhang et al.[150] found that downregulation of anaerobic glycolysis is required for the promotion of RIG-I-like receptor (RLR)-induced production of type I IFN. However, without sufficient surface expression of monocarboxylate transporter 1 (MCT1), cells stimulated upon poly (I:C) transfection were unable to properly upregulate IFN-β expression induced by lactate dehydrogenase A (LDHA) inhibitors, indicating that lactate uptake is essential for the inhibitory effect of glycolysis on RLR signaling.

MCT1 is only minimally expressed in the cell membrane of macrophages[151,152] while MCT4 is required for macrophage activation by TLR2 and TLR4 agonists, where it helps sustain high glycolysis and expression of proinflammatory mediators[153].

In the high-lactate tumor microenvironment, the cellular uptake of lactate produced by tumor cells is mediated by MCTs in tumor-associated macrophages (TAMs), where it promotes polarization towards the M2-like phenotype and the resulting increased secretion of vascular endothelial growth factor (VEGF) through hypoxia-inducible factor 1-alpha (HIF-1α)[139]. The information reviewed above lactate transporters involved in immune cells are summarized in Table 1.

6. Metals ion transporters in immune cells metabolism

In addition to the essential roles of the transporters of various metabolic substrates, metal ion transporters are also indispensable for cells of the immune system to execute their functions as well as maintain their metabolic homeostasis. In addition to their well-known roles as cofactors of cellular proteins, metal ions are also involved in cell growth, as well as signal transduction during the immune response and cytokine production, which are tightly regulated by corresponding ion transporters. Studies on these transporters will promote a better understanding of the functions of different metal ions in the immune system. The information reviewed above metal ion transporters involved in immune cells are summarized in Table 2[97−99,154-174].

6.1. *Zinc transporters-mediated zinc homeostasis*

As an indispensable component of over 300 different enzymes, zinc (Zn^{2+}) participates in scores of essential biochemical processes in addition to its structural roles[175,176]. Zinc released from internal stores may act as a second massager to promote cellular mobility[177]. Many zinc-related enzymes and metalloproteins are present in immune cells. Zinc deficiency leads to impaired immune responses both in innate immunity and antibody-mediated adaptive immunity. In zinc-deficient pro-myeloid cells, interleukin (IL)-1β and tumor necrosis factor alpha (TNFα) are upregulated, due to improved posttranscriptional processing *via* nicotinamide adenine dinucleotide phosphate (NADPH), ROS-mediated redox signaling, and the activation of the p38 mitogen-activated protein kinase (MAPK) phosphorylation mechanism[178]. Consistent with these observations, zinc deficiency increases the phagocytosis and oxidative burst in human peripheral blood mononuclear cells, whereas the production of TNF-α and IL-6 is reduced after zinc deprivation for three days[178]. In zinc-deficient mice, T cells show more apoptosis and impaired thymulin signaling, which is rescued by zinc supplementation. High levels of zinc supplementation, about four times the physiological concentration, suppress the alloreactivity of mixed lymphocytes[179]. As indicated, zinc performs its function in a concentration-dependent manner, which reflects its important roles in a complex network of cellular activities.

The SLC39A (zrt/irt-like proteins; ZIP) family and SLC30A (cation diffusion; ZnT) Zn^{2+} family are two major Zn^{2+} transporters families. The 14 SLC39A family members mediate the influx of zinc from the extracellular or luminal side into the cytoplasm and the 10 identified SLC30A family members mediate the efflux of zinc[154]. Their activity is tightly correlated with the immune system because of the essential status of zinc. *SLC39A7* encodes the ZIP7 protein, which is expressed ubiquitously regulating the influx of zinc from the Golgi or endoplasmic reticulum (ER) into the cytosol[180,181] (Fig. 2[156,182−185]). Multiple loss of function alleles of *SLC39A7* result in a human immunodeficiency syndrome featured by reduced B cell signaling at the positive selection checkpoints[156]. Developing B cells are prone to be affected by partial *SLC39A7* deficiency, which is reflected in impeded development beyond the pre-B cell stage[156]. Since the B cell receptor (BCR)-initiated pathways are mediated by various kinases and phosphatases[186], the inhibitory effect of zinc on phosphatases is likely the proximal cause of impaired BCR signaling (Fig. 2). Recently, a compound has been identified in a drug screen that is able to rescue the impairment of cell proliferation and endoplasmic reticulum stress caused by ZIP7 ablation in human osteosarcoma cell line MG-63 in a zinc-independent manner[187]. This makes ZIP7 a potential therapeutic target in diseases related to zinc dysregulation. Similar to *SLC39A7*, ZIP10, encoded by *SLC39A10*, is another zinc transporter that regulates BCR transduction. When stimulated with IL-7, the signal transducer and activator of transcription (STAT), like STAT5, are

Table 2 Properties and functions of ion transporters and other essential transporters in immunometabolism.

Gene	Alias	Transport mechanism	Substrate	Inhibitor/blocker	Comment	Polymorphism	Ref.
SLC39A7	*ZIP7*, *Ke-4*	Inward-open and outward-open conformation changes	Zinc, manganese	NVS-ZP7-4 (IC_{50} = 0.13 μmol/L)	• SLC39A7 is essential for the Zn^{2+} mediated BCR signaling.	–	154–156
SLC39A10	*ZIP10*	Inward-open and outward-open conformation changes	Zinc	–	• SLC39A10 regulates the BCR transduction as a positive regulator of CD45R. • SLC39A10-mediated zinc homeostasis is needed for the survival of macrophages and monocytes in the LPS-induced inflammatory response.	–	154
SLC30A8	*ZnT8*	Zn^{2+}/H^{+} exchanger	Zinc	–	ZnT8 acts as an immunogen in autoimmune diabetes in type I diabetes (T1D).	The type 1 diabetes autoimmune response to *SLC30A8* is focused on a few key epitopes, two of which are defined by the polymorphic AA 325 residue.	157,158
SLC41A1	*MgtE*	Na^{+}/Mg^{2+} co-transporter driving by electrochemical gradient of Na^{+}	Mg^{2+}, Fe^{2+}, Zn^{2+}, Cu^{2+}, Co^{2+}, and Cd^{2+}	Amiloride (K_i = ~7 μmol/L), quinidine, or imipramine	SLC42A1 and SLC41A2 regulate Mg^{2+} homeostasis cooperated with other Mg^{2+} transporters and ion channels in the lymphocytes.	–	159,160
SLC41A2	*SLC41A1-L1*	Putative Mg^{2+} channel	Mg^{2+}, Ba^{2+}, Ni^{2+}, Co^{2+}, Fe^{2+}, and Mn^{2+}	Ca^{2+} (high concentration)		–	161
SLC22A5	*OCTN2*	Na^{+}/L-carnitine co-transporter	Acetyl-L-carnitine, L-carnitine	Cefepime, cefoselis, cephaloridine, emetine (IC_{50} = 4.2 μmol/L), uinidine and verapamil	OCTN2 mediated L-carnitine transport is needed for the differentiation from the monocytes to the macrophages in human.	–	162,163
SLC4A7	*NBC3*, *SBC2*	Na^{+}/HCO_3^{-} co-transporter	Na^{+}, HCO_3^{-}	5-(*N*-Ethyl-*N*-isopropyl)-amiloride (EIPA)	SLC4A7 maintains the intracellular pH to facilitate the phagosome acidification upon macrophages differentiation.	–	164,165
SLCO2A1	*PGT* *OATP2A1*	Sodium-dependent, high-affinity carnitine transporter	Eicosanoid, prostaglandins	Bromocresol green (pK_i = ~5.4), bromsulphthalein (pK_i = ~5.2)	SLCO2A1 modulates the removal of neutrophils in the inflammatory sites through mediating the prostaglandin E2 (PGE2) secretion by macrophages.	–	166,167
SLC11A1	*LSH*, *NRAMP*, *NRAMP1*	Proton-coupled divalent metal ion transporter	Fe^{2+}, Mn^{2+} and other divalent metal ions	PP2 (The phosphorylation of SLC11A1 is completely blocked)	SLC11A1 could protect macrophages from the reactive oxygen species and deny the cations to the pathogens to limit their growth.	Chronic hyperactivation of macrophages associated with a polymorphism in the promoter of human *SLC11A1* is functionally linked to autoimmune disease	168–170

(*continued on next page*)

Table 2 (*continued*)

Gene	Alias	Transport mechanism	Substrate	Inhibitor/blocker	Comment	Polymorphism	Ref.
SLC15A2	*PEPT2*	H^+-coupled oligopeptide cotransporter	5-Aminolevulinic acid, dipeptides, protons, tripeptides	Lys[Z(NO2)]-Pro[a], Lys [Z(NO2)]-Lys [Z(NO2)][a] (pK_i = 8.0), amoxicillin (K_i = ~733 μmol/L)	• SLC15A2 and SLC15A4 collaborate to uptake bacterial-derived ligands into the cytosol of macrophages, thereby enhancing the production of pro-inflammatory cytokines. • SLC15A4 is crucial for the Toll-like receptor triggered type I interferon (IFN-I) production in the plasmacytoid dendritic cells (pDCs) and contributes to the pathogenesis of lupus-like autoimmunity.	– susceptibility.	169,171–174
SLC15A4	*PHT1*, *PTR4*	H^+-coupled oligopeptide cotransporter	L-Histidine, carnosine	–			97–99

—Not applicable.
[a]Z(NO2)]: 4-nitrobenzyloxycarbonyl.

activated in the early B cells. Then the signal upregulating of ZIP10 promotes early B-cell survival by inhibiting caspase activation (Fig. 2). ZIP10 also functions as a positive regulator of CD45R that alters the signal strength of the BCR[188] (Fig. 2). In innate immunity, *Slc39a10*-deficency leads to reduced numbers of macrophages and monocytes in the LPS-induced inflammatory response, which is caused by increased mortality in a P53-dependent manner[189]. However, how reduced cytoplasmic zinc levels lead to the accumulation of P53 and apoptosis-inducing factor (AIF), and whether there is a complementary function of other zinc transporters, which may explain the considerable number of normal infiltrating macrophages in inflammatory responses, is still not fully clarified. Although the relationship between Zn^{2+} deficiency and cell death has been studied in detail, these findings highlight the critical roles of zinc transporters in the immune response as well as the potential drug targets in some human diseases, like thymic atrophy and lymphopenia, which are tightly related to zinc deficiency[190,191].

Local zinc accumulation mediated by SLC39A6 (ZIP6) in dendritic cells (DC) and T cells can indirectly activate the TCR-activation pathway, followed by cell proliferation and cytokine production[192]. The zinc transporters ZIP6 and ZIP10 are downregulated, while the zinc the exporters ZnT1 and ZnT6 are upregulated in the DCs when treated with LPS, thereby promoting their maturation[193]. SLC39A8 (ZIP8) is highly induced in response to LPS and TNFα, leading to a rapid increase of intracellular zinc levels[194]. The upregulation of ZIP8 is directly induced by transcription factor NF-κB that is activated through phosphorylation when the IκB kinase (IKK) complex is activated in the toll-like receptor (TLR) signaling pathway. Conversely, the increased zinc concentration negatively regulates NF-κB by inhibiting the IκB kinase beta subunit (IKKβ) in the kinase domain, thus suppressing inflammation and improving survival of the immune cells[194]. This feedback effect of the zinc transporter in innate immunity shows how the action of zinc coordinates with the immune responses to protect the host cells. However, before a specialized role of ZIP8 can be postulated, more evidence is needed to determine its correlation with other zinc transporters in certain immune responses and the regulatory relationship with other inhibitors of the NF-κB pathway. The roles of SLC30A (ZnT) family members in immunity are less studied, but some of them are nevertheless known to be involved in the maintenance of metabolic homeostasis. Zinc transporter protein member 8 (ZnT8; SLC30A8), an islet-specific cell-membrane zinc transporter involved in the assembly of insulin hexamers[195], is reported as a major autoantigen and a potential diagnostic marker for type 1 diabetes, that is detected in different populations at varying levels[157,196]; while ZnT5, which is responsible for NF-κB-dependent cytokine production in mast cells, has been associated with the allergic response[197]. Since the mRNA level of *ZnT1*, *ZnT4*, *ZnT6*, and *ZnT7* are strongly reduced in T cells following stimulation by phytohemagglutinin, it stands to reason that the downregulation of the ZnTs can be used as an intervention to maintain the intracellular zinc concentration during T cell activation[198]. However, the regulatory mechanisms underpinning zinc homeostasis still remain to be clearly elucidated.

6.2. *Roles of magnesium transporters in regulating immune cell growth*

As the most abundant divalent cation in cells, the concentration of Mg^{2+}, ranges between 14 and 20 mmol/L[199], but is more typically

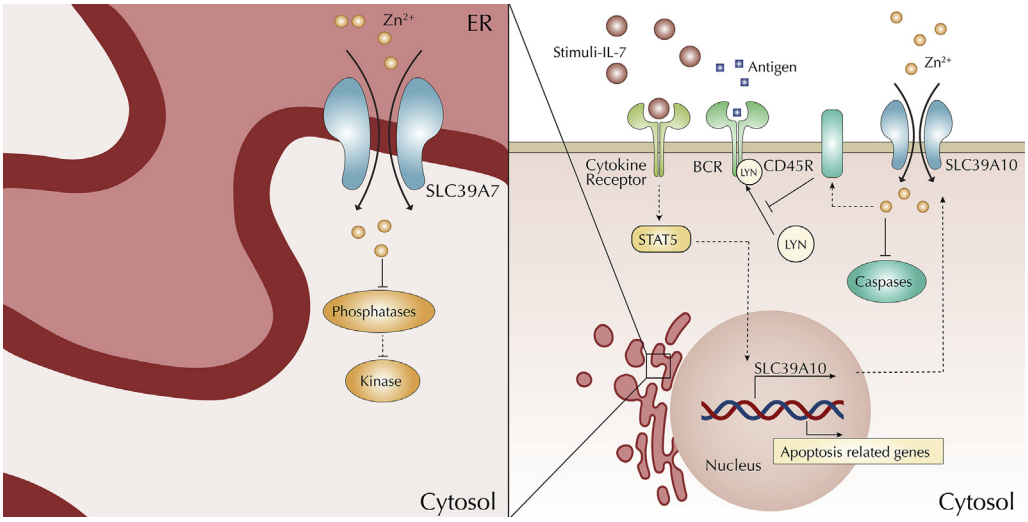

Figure 2 The roles of zinc transporters in B cells of different stages. In the developmental stages of early B cells, STAT5 activation in the BCR signaling pathway triggered by cytokines like IL-7 upregulates SLC39A10, which subsequently increases the cytoplasmic zinc levels. As an inhibitor of effort caspases such as caspase 3 and caspase 9[182,183], zinc may regulate the early B cell survival, which is consistent with the phenomenon that SLC39A10 deficiency leads to a reduced population of both pro- and pre-B-cell, accompanied with reduced intracellular zinc concentrations[184]. In mature B cells, SLC39A10 acts as a positive regulator of CD45R, which has inhibitory effect on the Lyn by dephosphorylating regulatory tyrosine residues of the Lyn in a dynamic behavior[185]. In the pre- and immature-B cells, SLC39A7 deficiency is associated with reduced cytoplasm zinc level. Since zinc is a negative regulator of phosphatases, their activity is elevated in SLC39A7-deficient B cells, which inhibits kinase activity and consequently leads to impaired BCR-dependent signaling. This impairment finally leads to reduced numbers of pre-, immature, and mature B cells, with a developmental block in pre-B stage[156]. STAT5, signal transducer and activator of transcription 5; BCR, B cell receptor; IL-7, interleukin 7; CD45R, a receptor-type protein tyrosine phosphatase; Lyn, tyrosine-protein kinase.

within the range of 0.3−1.0 mmol/L[200]. In addition to its well-known functions as a structural partner of some phosphates and nucleic acids, with positive or negative regulatory effects on enzymes, and its function as a modulator of cell proliferation, cell cycle progression, and differentiation, Mg^{2+} is also required for the regulation of the immune system[201]. During the immune response, magnesium acts as a co-factor for immunoglobulin synthesis, antibody-dependent cytolysis, IgM lymphocyte binding, T−B cell adherence in adaptive immunity, the response of macrophages to lymphokines in innate immunity, and C3 convertase in the complement system[202]. Studies of the regulation of Mg^{2+} homeostasis proposed SLC41A1 and SLC41A2 as two key Mg^{2+} transporters. SLC41A1 is ubiquitously expressed in most tissues and lymphoid cell lines, and it functions as an Mg^{2+}/Na^{+} exchanger[203], while SLC41A2 is expressed in various immune cells as well. The overexpression of SLC41A1 and SLC41A2 in lymphocytes partially rescued the reduction of cell growth which caused by the deletion of other Mg^{2+} permeable ion channels, like TRPM7 (transient receptor potential cation channel subfamily M member 7), in vertebrate DT-40 cells[159,204]. This indicates that both SLC41A1 and SLC41A2 are significant players in regulating the Mg^{2+} homeostasis, thereby maintaining the normal growth of lymphocytes.

7. Other transporters in the inflammatory responses

7.1. Role of SLC22A5-mediated L-carnitine transport in immune-cell differentiation

Some of the SLC22 transporter family members are the main membrane proteins that mediate the transport of L-carnitine[205]. Since L-carnitine acts as a mediator of the import of long-chain fatty acids into the mitochondria to be oxidized for energy production, regulating the concentration of L-carnitine by SLC22 family members is vital for the normal functioning of cells and tissues. L-Carnitine has been confirmed to act as a mediator of immune function during the differentiation of human monocytes into macrophages[163]. Human SLC22A5 is a Na^{+}/carnitine cotransporter which transports acetyl-L-carnitine and buturyl-L-carnitine as well, while human SLC22A4 is another L-carnitine transporter with lower affinity[206]. The human genes encoding *SLC22A5* and *SLC22A4* are both located on chromosome 5q in a locus that is associated with many inflammatory diseases[205]. Many studies suggest that carnitine transport deficiency might play a role in the pathogenesis of Crohn's disease[207−209]. These transporter functions indicate that the cell growth, differentiation, and some other substantial changes that happen in immune cells are likely dependent on solute carriers to various degrees.

7.2. The essential role of SLC4A7 during phagosome acidification

Macrophages normally undergo frequent metabolic changes to execute their mission as front-line immune cells that surveil and clear deleterious substances or pathogens which end up being cleared through phagocytosis. The regulation of the intracellular and extracellular pH is essential for the normal function of macrophages during immune responses. CO_2 and HCO_3^- are general and pivotal components in the body's buffering system. The maintenance of the intracellular level of HCO_3^- correlates with the intracellular pH. The electroneutral Na, HCO_3^--cotransporter NBCn1 coded by *SLC4A7* is stimulated by CO_2/HCO_3^- transportation associated with Na^{+}[210]. NBCn1 transports the Na^{+} and HCO_3^- into the cytoplasm at the ratio of $1Na^{+}$:$1HCO_3^-$[210]. Upon

macrophage differentiation, the bicarbonate transporter SLC4A7 is strongly induced and acts as a critical driver of phagosome acidification. Loss of SLC4A7 would lead to cytoplasmic acidification, which perturbs phagosome maturation and pathogen clearance[165]. Homeostasis is a basic necessity for cells to fully carry out their functions.

In addition, CRISPR/Cas9 targeting scores of solute transporters followed by the sequencing of the macrophages undergoing phagocytosis and phagosome acidification or not highlights the key role of SLC4A7 in the immune function of macrophages[165]. This approach provides lessons for further exploring the association between solute transporters and cellular processes. However, since the screening is carried out in cell lines, further *in vivo* evidence is also needed.

7.3. *The role of SLCO2A1 in PEG2 exocytosis from macrophages*

Prostaglandin E2 (PEG2), which is partially regulated by the transporter OATP2A1/SLCO2A1, a member of the organic anion transporting polypeptide superfamily, is able to transport PEG2 directionally. It is also involved in maintaining homeostasis by mediating the removal of neutrophils from the sites of inflammation[167]. Based on a deficient mouse model, OATP2A is definitely responsible for the partial PEG2 exocytosis from macrophages in inflammatory responses[211]. However, to what extent this transporter functions when the body is facing a certain stimulus still needs to be addressed. Given that PEG2 contributes partially to the clearance of neutrophils, the signal pathway which OATP2A1 participates in is a potential drug target for neutrophil associated immune diseases. Some other members of the SLCO superfamily may have links to the immune responses as well, since SLCO2B1, SLCO3A1, and SLCO4A1 are expressed in monocytes and antigen-presenting cells, macrophages, and dendritic cells, among which SLCO2B1 and SLCO4A1 are notably more highly expressed than in the monocytes and dendritic cells, which indicates that they may have a role in macrophage maturation and activation[212]. Further evidence is needed to elucidate the functions of these transporters in the immune response.

7.4. *SLC11A1 in phagosome-mediated parasite immunity*

Solute carrier family 11 member A1 (SLC11A1) is a proton/divalent cation antiporter that is recruited to the membrane of lysosomes upon the phagocytosis of parasites[213]. This transporter exerts pleiotropic effects in the defense against parasites and other pathogens. The deprivation of divalent cations, like ferrous iron, manganese, and zinc, limits the amount of divalent metals available to the pathogen, which inhibits its growth and makes it susceptible to the reactive oxidants and other immune-cell effector molecules[214]. The enhanced expression of SLC11A1 in innate lymphocytes is due to the increased IFN-γ expression in monocytes followed by the production of IL-12 and other cytokines, which in turn stimulate IFN-γ expression[215]. Moreover, the increased production of nitric oxide (NO), IL-12, and TNF-α correlates the enhanced expression of SLC11A1 in parasite-engulfing macrophages[213]. The activation of SLC11A1 could also confer resistance against pathogens in the phagosomes mediated by iron-dependent NADPH oxidase activity and NO formation[216].

7.5. *SLC15A2 and SLC15A4 in innate immunity against bacteria*

Solute carrier family 15 (SLC15) members are H^+-coupled oligopeptide cotransporters. SLC15A2 (also known as PEPT2) and SLC15A4 (also known as PHT1) are two representatives that transport nucleotide-binding oligomerization domain containing 2 (NOD2) ligands in the plasma membrane of epithelial cells and innate immune cells, like macrophages and dendritic cells, respectively[217,218]. NOD2 is a nucleotide-binding oligomerization domain protein that acts as a pattern-recognition receptor to trigger a series of pathogen-fighting mechanisms when detecting the presence of bacterially derived products[172]. Transcription factors NF-κB and AP-1 are induced in the NOD signaling pathway, which in turn enhances the production of pro-inflammatory cytokines[219]. SLC15A2 and SLC15A4 collaborate to import bacteria-derived ligands into the cytosol of macrophages, thereby enhancing the production of pro-inflammatory cytokines[218].

8. Links to therapeutics and human disease

Based on the importance of the metabolic demands in immune cell activation, proliferation, and differentiation, nutrient transporters may be new targets to modulate the immune response.

It has been demonstrated that metabolic alterations of T cells are associated with immune dysfunctions in several autoimmune diseases, such as rheumatoid arthritis (RA), multiple sclerosis (MS), and systemic lupus erythematosus (SLE)[220,221]. Alteration of the glucose metabolism by inhibiting GLUTs might be a promising strategy to reduce the proliferation and hyperactivation of autoreactive T cells in these autoimmune diseases[222].

Inhibition of lactate production has been proposed as an approach to derepress anti-tumor immunity. Several specific inhibitors targeting MCT1 and MCT2 have been investigated in the preclinical stages. The MCT1 and MCT2 inhibitor AR-C155858 has been found to inhibit T cell activation and suppress the immune response by balancing lactate export[223]. AZD3965, another MCT1 and MCT2 inhibitor, is currently tested in a phase I trial targeting advanced-stage prostate cancer, diffuse large B cell lymphoma, and Burkitt's lymphoma (NCT01791595)[224].

The results of several recent clinical studies revealed that targeting glucose and/or lactate metabolism is an appealing therapeutic strategy for tumors. However, such approaches might simultaneously abrogate the immune response by reducing the numbers of tumor-infiltrating T cell and their cytotoxicity due to energy deficiency[138,225]. Therefore, further studies on targeting nutrient transporters are required to find the balance between effective anti-tumor immune responses and blunted tumorigenesis.

9. Conclusions

Importantly, immunometabolism is critical for determining immunophenotypes and responses, and nutrient transporters have emerged as excellent targets to regulate the metabolic phenotypes of immune cells. As increasing numbers of studies have been conducted to understand how transporters perform their immunomodulatory functions, a number of limitations have impeded progress in this research area.

Firstly, there are a number of transporters without clearly known endogenous substrates, and characterizing their function in immunity can be difficult. For instance, the substrates and functional regulation of GLUT1−5 have already been substantially investigated, but only a handful of articles have been published on the more recently discovered glucose transporters GLUT6−12. Secondly, genetic gain- or loss-of-function studies of each of the newly discovered transporters will undoubtedly contribute to revealing their functions in immune cells. However, the conclusions may presumably be confounded by compensatory efflux upregulation of endogenous transporters with overlapping specificities or by metabolic perturbation.

A more detailed knowledge of the substrates, functions and regulation of the recently discovered transporter proteins in immune cells in response to different stimuli may provide important clues and yield new targets for therapy.

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Author contributions

Ligong Chen, Wenxin Song, and Danyuan Li wrote the manuscript. Wenxin Song and Lei Tao draw the illustrations. Ligong Chen, Wenxin Song, Danyuan Li, Qi Luo, and Lei Tao contributed to the literature search. Ligong Chen and Qi Luo edited the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Appendix A. Supporting information

Supporting data to this article can be found online at https://doi.org/10.1016/j.apsb.2019.12.006.

References

1. Lin L, Yee SW, Kim RB, Giacomini KM. SLC transporters as therapeutic targets: emerging opportunities. *Nat Rev Drug Discov* 2015;**14**:543−60.
2. DeGorter MK, Xia CQ, Yang JJ, Kim RB. Drug transporters in drug efficacy and toxicity. *Annu Rev Pharmacol Toxicol* 2012;**52**:249−73.
3. Emami Riedmaier A, Nies AT, Schaeffeler E, Schwab M. Organic anion transporters and their implications in pharmacotherapy. *Pharmacol Rev* 2012;**64**:421−49.
4. Liang Y, Li S, Chen L. The physiological role of drug transporters. *Protein Cell* 2015;**6**:334−50.
5. Morrissey KM, Wen CC, Johns SJ, Zhang L, Huang SM, Giacomini KM. The UCSF−FDA TransPortal: a public drug transporter database. *Clin Pharmacol Ther* 2012;**92**:545−6.
6. Gottesman MM, Ambudkar SV. Overview: ABC transporters and human disease. *J Bioenerg Biomembr* 2001;**33**:453−8.
7. César-Razquin A, Snijder B, Frappier-Brinton T, Isserlin R, Gyimesi G, Bai X, et al. A call for systematic research on solute carriers. *Cell* 2015;**162**:478−87.
8. Rives ML, Javitch JA, Wickenden AD. Potentiating SLC transporter activity: emerging drug discovery opportunities. *Biochem Pharmacol* 2017;**135**:1−11.
9. Hediger MA, Romero MF, Peng JB, Rolfs A, Takanaga H, Bruford EA. The ABCs of solute carriers: physiological, pathological and therapeutic implications of human membrane transport proteins. *Pflugers Arch* 2004;**447**:465−8.
10. Chen L, Shu Y, Liang X, Chen EC, Yee SW, Zur AA, et al. OCT1 is a high-capacity thiamine transporter that regulates hepatic steatosis and is a target of metformin. *Proc Natl Acad Sci U S A* 2014;**111**:9983−8.
11. Chen L, Yee SW, Giacomini KM. OCT1 in hepatic steatosis and thiamine disposition. *Cell Cycle* 2015;**14**:283−4.
12. Chen Y, Li S, Brown C, Cheatham S, Castro RA, Leabman MK, et al. Effect of genetic variation in the organic cation transporter 2 on the renal elimination of metformin. *Pharmacogenetics Genom* 2009;**19**:497−504.
13. Song W, Luo Q, Zhang Y, Zhou L, Liu Y, Ma Z, et al. Organic cation transporter 3 (Oct3) is a distinct catecholamines clearance route in adipocytes mediating the beiging of white adipose tissue. *PLoS Biol* 2019;**17**:e2006571.
14. Ji L, Zhao X, Zhang B, Kang L, Song W, Zhao B, et al. Slc6a8-mediated creatine uptake and accumulation reprogram macrophage polarization *via* regulating cytokine responses. *Immunity* 2019;**51**:272−84.
15. Inman M. Immune cells strike a balance to avoid autoimmune disease. *PLoS Biol* 2006;**4**:e393.
16. MacIver NJ, Jacobs SR, Wieman HL, Wofford JA, Coloff JL, Rathmell JC. Glucose metabolism in lymphocytes is a regulated process with significant effects on immune cell function and survival. *J Leukoc Biol* 2008;**84**:949−57.
17. Chen H, Jiang Z. The essential adaptors of innate immune signaling. *Protein Cell* 2013;**4**:27−39.
18. Jung J, Zeng H, Horng T. Metabolism as a guiding force for immunity. *Nat Cell Biol* 2019;**21**:85−93.
19. Davies LC, Jenkins SJ, Allen JE, Taylor PR. Tissue-resident macrophages. *Nat Immunol* 2013;**14**:986−95.
20. Biswas SK, Mantovani A. Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm. *Nat Immunol* 2010;**11**:889−96.
21. Murray PJ, Allen JE, Biswas SK, Fisher EA, Gilroy DW, Goerdt S, et al. Macrophage activation and polarization: nomenclature and experimental guidelines. *Immunity* 2014;**41**:14−20.
22. Litman GW, Rast JP, Fugmann SD. The origins of vertebrate adaptive immunity. *Nat Rev Immunol* 2010;**10**:543−53.
23. Parra D, Takizawa F, Sunyer JO. Evolution of B cell immunity. *Annu Rev Anim Biosci* 2013;**1**:65−97.
24. Buckley RH. Molecular defects in human severe combined immunodeficiency and approaches to immune reconstitution. *Annu Rev Immunol* 2004;**22**:625−55.
25. Bantug GR, Galluzzi L, Kroemer G, Hess C. The spectrum of T cell metabolism in health and disease. *Nat Rev Immunol* 2018;**18**:19−34.
26. Ellmeier W, Sawada S, Littman DR. The regulation of CD4 and CD8 coreceptor gene expression during T cell development. *Annu Rev Immunol* 1999;**17**:523−54.
27. Zhu J, Yamane H, Paul WE. Differentiation of effector CD4 T cell populations. *Annu Rev Immunol* 2010;**28**:445−89.
28. Kaech SM, Cui W. Transcriptional control of effector and memory $CD8^+$ T cell differentiation. *Nat Rev Immunol* 2012;**12**:749−61.
29. Vinuesa CG, Tangye SG, Moser B, Mackay CR. Follicular B helper T cells in antibody responses and autoimmunity. *Nat Rev Immunol* 2005;**5**:853−65.

30. Freemerman AJ, Johnson AR, Sacks GN, Milner JJ, Kirk EL, Troester MA, et al. Metabolic reprogramming of macrophages: glucose transporter 1 (GLUT1)-mediated glucose metabolism drives a proinflammatory phenotype. *J Biol Chem* 2014;**289**: 7884−96.
31. Jacobs SR, Herman CE, Maciver NJ, Wofford JA, Wieman HL, Hammen JJ, et al. Glucose uptake is limiting in T cell activation and requires CD28-mediated Akt-dependent and independent pathways. *J Immunol* 2008;**180**:4476−86.
32. Araki K, Turner AP, Shaffer VO, Gangappa S, Keller SA, Bachmann MF, et al. mTOR regulates memory CD8 T-cell differentiation. *Nature* 2009;**460**:108−12.
33. Man K, Miasari M, Shi W, Xin A, Henstridge DC, Preston S, et al. The transcription factor IRF4 is essential for TCR affinity-mediated metabolic programming and clonal expansion of T cells. *Nat Immunol* 2013;**14**:1155−65.
34. Palmer CS, Ostrowski M, Balderson B, Christian N, Crowe SM. Glucose metabolism regulates T cell activation, differentiation, and functions. *Front Immunol* 2015;**6**:1.
35. Frauwirth KA, Thompson CB. Regulation of T lymphocyte metabolism. *J Immunol* 2004;**172**:4661−5.
36. Warburg O. On the origin of cancer cells. *Science* 1956;**123**:309−14.
37. Thorens B, Mueckler M. Glucose transporters in the 21st century. *Am J Physiol Endocrinol Metab* 2010;**298**:E141−5.
38. Swainson L, Kinet S, Manel N, Battini JL, Sitbon M, Taylor N. Glucose transporter 1 expression identifies a population of cycling $CD4^+$ $CD8^+$ human thymocytes with high CXCR4-induced chemotaxis. *Proc Natl Acad Sci U S A* 2005;**102**:12867−72.
39. Cretenet G, Clerc I, Matias M, Loisel S, Craveiro M, Oburoglu L, et al. Cell surface Glut1 levels distinguish human CD4 and CD8 T lymphocyte subsets with distinct effector functions. *Sci Rep* 2016;**6**: 24129.
40. Basu S, Hubbard B, Shevach EM. Foxp3-mediated inhibition of Akt inhibits Glut1 (glucose transporter 1) expression in human T regulatory cells. *J Leukoc Biol* 2015;**97**:279−83.
41. Gerriets VA, Kishton RJ, Nichols AG, Macintyre AN, Inoue M, Ilkayeva O, et al. Metabolic programming and PDHK1 control $CD4^+$ T cell subsets and inflammation. *J Clin Investig* 2015;**125**:194−207.
42. Nath MD, Ruscetti FW, Petrow-Sadowski C, Jones KS. Regulation of the cell-surface expression of an HTLV-I binding protein in human T cells during immune activation. *Blood* 2003;**101**:3085−92.
43. Shankar SS, Dubé MP. Clinical aspects of endothelial dysfunction associated with human immunodeficiency virus infection and antiretroviral agents. *Cardiovasc Toxicol* 2004;**4**:261−9.
44. Loisel-Meyer S, Swainson L, Craveiro M, Oburoglu L, Mongellaz C, Costa C, et al. Glut1-mediated glucose transport regulates HIV infection. *Proc Natl Acad Sci U S A* 2012;**109**:2549−54.
45. Macintyre AN, Gerriets VA, Nichols AG, Michalek RD, Rudolph MC, Deoliveira D, et al. The glucose transporter Glut1 is selectively essential for CD4 T cell activation and effector function. *Cell Metabol* 2014;**20**:61−72.
46. Cao Y, Rathmell JC, Macintyre AN. Metabolic reprogramming towards aerobic glycolysis correlates with greater proliferative ability and resistance to metabolic inhibition in CD8 *versus* CD4 T cells. *PLoS One* 2014;**9**:e104104.
47. Abdel Aziz N, Nono JK, Mpotje T, Brombacher F. The $Foxp3^+$ regulatory T-cell population requires IL-4Rα signaling to control inflammation during helminth infections. *PLoS Biol* 2018;**16**:e2005850.
48. Corvaisier M, Delneste Y, Jeanvoine H, Preisser L, Blanchard S, Garo E, et al. IL-26 is overexpressed in rheumatoid arthritis and induces proinflammatory cytokine production and Th17 cell generation. *PLoS Biol* 2012;**10**:e1001395.
49. Amarnath S, Costanzo CM, Mariotti J, Ullman JL, Telford WG, Kapoor V, et al. Regulatory T cells and human myeloid dendritic cells promote tolerance *via* programmed death ligand-1. *PLoS Biol* 2010;**8**:e1000302.
50. Beier UH, Angelin A, Akimova T, Wang L, Liu Y, Xiao H, et al. Essential role of mitochondrial energy metabolism in $Foxp3^+$ T-regulatory cell function and allograft survival. *FASEB J* 2015;**29**: 2315−26.
51. Michalek RD, Gerriets VA, Jacobs SR, Macintyre AN, MacIver NJ, Mason EF, et al. Cutting edge: distinct glycolytic and lipid oxidative metabolic programs are essential for effector and regulatory $CD4^+$ T cell subsets. *J Immunol* 2011;**186**:3299−303.
52. Shi LZ, Wang R, Huang G, Vogel P, Neale G, Green DR, et al. HIF1alpha-dependent glycolytic pathway orchestrates a metabolic checkpoint for the differentiation of TH17 and Treg cells. *J Exp Med* 2011;**208**:1367−76.
53. Wieman HL, Wofford JA, Rathmell JC. Cytokine stimulation promotes glucose uptake *via* phosphatidylinositol-3 kinase/Akt regulation of Glut1 activity and trafficking. *Mol Biol Cell* 2007;**18**: 1437−46.
54. Wang C, Mayer JA, Mazumdar A, Fertuck K, Kim H, Brown M, et al. Estrogen induces *c-myc* gene expression *via* an upstream enhancer activated by the estrogen receptor and the AP-1 transcription factor. *Mol Endocrinol* 2011;**25**:1527−38.
55. Michalek RD, Gerriets VA, Nichols AG, Inoue M, Kazmin D, Chang CY, et al. Estrogen-related receptor-α is a metabolic regulator of effector T-cell activation and differentiation. *Proc Natl Acad Sci U S A* 2011;**108**:18348−53.
56. Kavanagh Williamson M, Coombes N, Juszczak F, Athanasopoulos M, Khan MB, Eykyn TR, et al. Upregulation of glucose uptake and hexokinase activity of primary human $CD4^+$ T cells in response to infection with HIV-1. *Viruses* 2018;**10**:E114.
57. Tannahill GM, Curtis AM, Adamik J, Palsson-McDermott EM, McGettrick AF, Goel G, et al. Succinate is an inflammatory signal that induces IL-1β through HIF-1α. *Nature* 2013;**496**:238−42.
58. Vats D, Mukundan L, Odegaard JI, Zhang L, Smith KL, Morel CR, et al. Oxidative metabolism and PGC-1beta attenuate macrophage-mediated inflammation. *Cell Metabol* 2006;**4**:13−24.
59. Odegaard JI, Ricardo-Gonzalez RR, Goforth MH, Morel CR, Subramanian V, Mukundan L, et al. Macrophage-specific PPARγ controls alternative activation and improves insulin resistance. *Nature* 2007;**447**:1116−20.
60. Newsholme P, Curi R, Gordon S, Newsholme EA. Metabolism of glucose, glutamine, long-chain fatty acids and ketone bodies by murine macrophages. *Biochem J* 1986;**239**:121−5.
61. Spolarics Z, Wu JX. Tumor necrosis factor alpha augments the expression of glucose-6-phosphate dehydrogenase in rat hepatic endothelial and Kupffer cells. *Life Sci* 1997;**60**:565−71.
62. Van den Bossche J, Baardman J, Otto NA, van der Velden S, Neele AE, van den Berg SM, et al. Mitochondrial dysfunction prevents repolarization of inflammatory macrophages. *Cell Rep* 2016; **17**:684−96.
63. Freemerman AJ, Zhao L, Pingili AK, Teng B, Cozzo AJ, Fuller AM, et al. Myeloid *Slc2a1*-deficient murine model revealed macrophage activation and metabolic phenotype are fueled by GLUT1. *J Immunol* 2019;**202**:1265−86.
64. Maedera S, Mizuno T, Ishiguro H, Ito T, Soga T, Kusuhara H. GLUT6 is a lysosomal transporter that is regulated by inflammatory stimuli and modulates glycolysis in macrophages. *FEBS Lett* 2019; **593**:195−208.
65. Byrne FL, Poon IK, Modesitt SC, Tomsig JL, Chow JD, Healy ME, et al. Metabolic vulnerabilities in endometrial cancer. *Cancer Res* 2014;**74**:5832−45.
66. Uldry M, Ibberson M, Hosokawa M, Thorens B. GLUT2 is a high affinity glucosamine transporter. *FEBS Lett* 2002;**524**: 199−203.
67. Takata K, Kasahara T, Kasahara M, Ezaki O, Hirano H. Erythrocyte/HEPG2-type glucose transporter is concentrated in cells of blood−tissue barriers. *Biochem Biophys Res Commun* 1990;**173**: 67−73.

68. Zhao FQ, Glimm DR, Kennelly JJ. Distribution of mammalian facilitative glucose transporter messenger RNA in bovine tissues. *Int J Biochem* 1993;**25**:1897−903.
69. Ung PM, Song W, Cheng L, Zhao X, Hu H, Chen L, et al. Inhibitor discovery for the human GLUT1 from homology modeling and virtual screening. *ACS Chem Biol* 2016;**11**:1908−16.
70. Wood TE, Dalili S, Simpson CD, Hurren R, Mao X, Saiz FS, et al. A novel inhibitor of glucose uptake sensitizes cells to FAS-induced cell death. *Mol Cancer Ther* 2008;**7**:3546−55.
71. Tuccinardi T, Granchi C, Iegre J, Paterni I, Bertini S, Macchia M, et al. Oxime-based inhibitors of glucose transporter 1 displaying antiproliferative effects in cancer cells. *Bioorg Med Chem Lett* 2013;**23**:6923−7.
72. Masson JJR, Cherry CL, Murphy NM, Sada-Ovalle I, Hussain T, Palchaudhuri R, et al. Polymorphism rs1385129 within Glut1 gene *SLC2A1* is linked to poor $CD4^+$ T cell recovery in antiretroviral-treated HIV^+ individuals. *Front Immunol* 2018;**9**:900.
73. Colville CA, Seatter MJ, Jess TJ, Gould GW, Thomas HM. Kinetic analysis of the liver-type (GLUT2) and brain-type (GLUT3) glucose transporters in *Xenopus* oocytes: substrate specificities and effects of transport inhibitors. *Biochem J* 1993;**290**:701−6.
74. Haber RS, Weinstein SP, O'Boyle E, Morgello S. Tissue distribution of the human GLUT3 glucose transporter. *Endocrinology* 1993;**132**:2538−43.
75. Nelson J, Falk R. Phloridzin and phloretin inhibition of 2-deoxy-D-glucose uptake by tumor cells *in vitro* and *in vivo*. *Anticancer Res* 1993;**13**:2293−9.
76. Veal CD, Reekie KE, Lorentzen JC, Gregersen PK, Padyukov L, Brookes AJ. A 129-kb deletion on chromosome 12 confers substantial protection against rheumatoid arthritis, implicating the gene *SLC2A3*. *Hum Mutat* 2014;**35**:248−56.
77. Kasahara T, Kasahara M. Characterization of rat Glut4 glucose transporter expressed in the yeast *Saccharomyces cerevisiae*: comparison with Glut1 glucose transporter. *Biochim Biophys Acta* 1997;**1324**:111−9.
78. Rumsey SC, Daruwala R, Al-Hasani H, Zarnowski MJ, Simpson IA, Levine M. Dehydroascorbic acid transport by GLUT4 xenopus oocytes and isolated rat adipocytes. *J Biol Chem* 2000;**275**:28246−53.
79. Doege H, Bocianski A, Joost HG, Schürmann A. Activity and genomic organization of human glucose transporter 9 (GLUT9), a novel member of the family of sugar-transport facilitators predominantly expressed in brain and leucocytes. *Biochem J* 2000;**350**:771−6.
80. Mackenzie B, Schäfer MK, Erickson JD, Hediger MA, Weihe E, Varoqui H. Functional properties and cellular distribution of the system A glutamine transporter SNAT1 support specialized roles in central neurons. *J Biol Chem* 2003;**278**:23720−30.
81. Kakuda T, Hinoi E, Abe A, Nozawa A, Ogura M, Yoneda Y. Theanine, an ingredient of green tea, inhibits [^{3}H] glutamine transport in neurons and astroglia in rat brain. *J Neurosci Res* 2008;**86**:1846−56.
82. Christensen HN. Role of amino acid transport and countertransport in nutrition and metabolism. *Physiol Rev* 1990;**70**:43−77.
83. McGivan JD, Pastor-Anglada M. Regulatory and molecular aspects of mammalian amino acid transport. *Biochem J* 1994;**299**:321−4.
84. Albers A, Broer A, Wagner CA, Setiawan I, Lang PA, Kranz EU, et al. Na^+ transport by the neural glutamine transporter ATA1. *Pflugers Arch* 2001;**443**:92−101.
85. Chaudhry FA, Schmitz D, Reimer RJ, Larsson P, Gray AT, Nicoll R, et al. Glutamine uptake by neurons: interaction of protons with system a transporters. *J Neurosci* 2002;**22**:62−72.
86. Hatanaka T, Huang W, Wang H, Sugawara M, Prasad PD, Leibach FH, et al. Primary structure, functional characteristics and tissue expression pattern of human ATA2, a subtype of amino acid transport system A. *Biochim Biophys Acta* 2000;**1467**:1−6.
87. Bevilacqua E, Bussolati O, Dall'Asta V, Gaccioli F, Sala R, Gazzola GC, et al. SNAT2 silencing prevents the osmotic induction of transport system A and hinders cell recovery from hypertonic stress. *FEBS Lett* 2005;**579**:3376−80.
88. Kekuda R, Prasad PD, Fei YJ, Torres-Zamorano V, Sinha S, Yang-Feng TL, et al. Cloning of the sodium-dependent, broad-scope, neutral amino acid transporter Bo from a human placental choriocarcinoma cell line. *J Biol Chem* 1996;**271**:18657−61.
89. Garaeva AA, Oostergetel GT, Gati C, Guskov A, Paulino C, Slotboom DJ. Cryo-EM structure of the human neutral amino acid transporter ASCT2. *Nat Struct Mol Biol* 2018;**25**:515−21.
90. Liu Y, Zhao T, Li Z, Wang L, Yuan S, Sun L. The role of ASCT2 in cancer: a review. *Eur J Pharmacol* 2018;**837**:81−7.
91. Chiu M, Sabino C, Taurino G, Bianchi MG, Andreoli R, Giuliani N, et al. GPNA inhibits the sodium-independent transport system L for neutral amino acids. *Amino Acids* 2017;**49**:1365−72.
92. Oppedisano F, Catto M, Koutentis PA, Nicolotti O, Pochini L, Koyioni M, et al. Inactivation of the glutamine/amino acid transporter ASCT2 by 1,2,3-dithiazoles: proteoliposomes as a tool to gain insights in the molecular mechanism of action and of antitumor activity. *Toxicol Appl Pharmacol* 2012;**265**:93−102.
93. Schulte ML, Dawson ES, Saleh SA, Cuthbertson ML, Manning HC. 2-Substituted *N*γ-glutamylanilides as novel probes of ASCT2 with improved potency. *Bioorg Med Chem Lett* 2015;**25**:113−6.
94. Schulte ML, Khodadadi AB, Cuthbertson ML, Smith JA, Manning HC. 2-Amino-4-bis (aryloxybenzyl) aminobutanoic acids: a novel scaffold for inhibition of ASCT2-mediated glutamine transport. *Bioorg Med Chem Lett* 2016;**26**:1044−7.
95. Schulte ML, Fu A, Zhao P, Li J, Geng L, Smith ST, et al. Pharmacological blockade of ASCT2-dependent glutamine transport leads to antitumor efficacy in preclinical models. *Nat Med* 2018;**24**:194−202.
96. Koeken V, Lachmandas E, Riza A, Matzaraki V, Li Y, Kumar V, et al. Role of glutamine metabolism in host defense against *Mycobacterium tuberculosis* infection. *J Infect Dis* 2019;**219**:1662−70.
97. Wilson MC, Meredith D, Fox JE, Manoharan C, Davies AJ, Halestrap AP. Basigin (CD147) is the target for organomercurial inhibition of monocarboxylate transporter isoforms 1 and 4: the ancillary protein for the insensitive MCT2 is EMBIGIN (gp70). *J Biol Chem* 2005;**280**:27213−21.
98. Voss DM, Spina R, Carter DL, Lim KS, Jeffery CJ, Bar EE. Disruption of the monocarboxylate transporter-4-basigin interaction inhibits the hypoxic response, proliferation, and tumor progression. *Sci Rep* 2017;**7**:4292.
99. Miranda-Goncalves V, Honavar M, Pinheiro C, Martinho O, Pires MM, Pinheiro C, et al. Monocarboxylate transporters (MCTs) in gliomas: expression and exploitation as therapeutic targets. *Neuro Oncol* 2013;**15**:172−88.
100. Ovens MJ, Davies AJ, Wilson MC, Murray CM, Halestrap AP. AR-C155858 is a potent inhibitor of monocarboxylate transporters MCT1 and MCT2 that binds to an intracellular site involving transmembrane helices 7−10. *Biochem J* 2010;**425**:523−30.
101. Sasaki S, Futagi Y, Kobayashi M, Ogura J, Iseki K. Functional characterization of 5-oxoproline transport *via* SLC16A1/MCT1. *J Biol Chem* 2015;**290**:2303−11.
102. Gopal E, Umapathy NS, Martin PM, Ananth S, Gnana-Prakasam JP, Becker H, et al. Cloning and functional characterization of human SMCT2 (SLC5A12) and expression pattern of the transporter in kidney. *Biochim Biophys Acta* 2007;**1768**:2690−7.
103. Arriza JL, Fairman WA, Wadiche JI, Murdoch GH, Kavanaugh MP, Amara SG. Functional comparisons of three glutamate transporter subtypes cloned from human motor cortex. *J Neurosci* 1994;**14**:5559−69.
104. Melzer N, Biela A, Fahlke C. Glutamate modifies ion conduction and voltage-dependent gating of excitatory amino acid transporter-associated anion channels. *J Biol Chem* 2003;**278**:50112−9.
105. Gendreau S, Voswinkel S, Torres-Salazar D, Lang N, Heidtmann H, Detro-Dassen S, et al. A trimeric quaternary structure is conserved in

bacterial and human glutamate transporters. *J Biol Chem* 2004;**279**:39505−12.
106. Abousaab A, Warsi J, Elvira B, Lang F. Caveolin-1 sensitivity of excitatory amino acid transporters EAAT1, EAAT2, EAAT3, and EAAT4. *J Membr Biol* 2016;**249**:239−49.
107. Lundin A, Delsing L, Clausen M, Ricchiuto P, Sanchez J, Sabirsh A, et al. Human iPS-derived astroglia from a stable neural precursor state show improved functionality compared with conventional astrocytic models. *Stem Cell Rep* 2018;**10**:1030−45.
108. Rimaniol AC, Mialocq P, Clayette P, Dormont D, Gras G. Role of glutamate transporters in the regulation of glutathione levels in human macrophages. *Am J Physiol Cell Physiol* 2001;**281**:C1964−70.
109. Rimaniol AC, Haïk S, Martin M, Le Grand R, Boussin FD, Dereuddre-Bosquet N, et al. Na^+-dependent high-affinity glutamate transport in macrophages. *J Immunol* 2000;**164**:5430−8.
110. Kawakami H, Tanaka K, Nakayama T, Inoue K, Nakamura S. Cloning and expression of a human glutamate transporter. *Biochem Biophys Res Commun* 1994;**199**:171−6.
111. Ryan RM, Kortt NC, Sirivanta T, Vandenberg RJ. The position of an arginine residue influences substrate affinity and K^+ coupling in the human glutamate transporter, EAAT1. *J Neurochem* 2010;**114**:565−75.
112. Krycer JR, Fazakerley DJ, Cater RJ, T KC, Naghiloo S, Burchfield JG, et al. The amino acid transporter, SLC1A3, is plasma membrane-localised in adipocytes and its activity is insensitive to insulin. *FEBS Lett* 2017;**591**:322−30.
113. Dixon SJ, Patel DN, Welsch M, Skouta R, Lee ED, Hayano M, et al. Pharmacological inhibition of cystine−glutamate exchange induces endoplasmic reticulum stress and ferroptosis. *Elife* 2014;**3**:e02523.
114. Gasol E, Jiménez-Vidal M, Chillarón J, Zorzano A, Palacin M. Membrane topology of system xc^- light subunit reveals a re-entrant loop with substrate-restricted accessibility. *J Biol Chem* 2004;**279**:31228−36.
115. Piani D, Fontana A. Involvement of the cystine transport system xc^- in the macrophage-induced glutamate-dependent cytotoxicity to neurons. *J Immunol* 1994;**152**:3578−85.
116. Sato H, Fujiwara K, Sagara J, Bannai S. Induction of cystine transport activity in mouse peritoneal macrophages by bacterial lipopolysaccharide. *Biochem J* 1995;**310**:547−51.
117. Bannai S, Sato H, Ishii T, Taketani S. Enhancement of glutathione levels in mouse peritoneal macrophages by sodium arsenite, cadmium chloride and glucose/glucose oxidase. *Biochim Biophys Acta* 1991;**1092**:175−9.
118. Piani D, Frei K, Do KQ, Cuenod M, Fontana A. Murine brain macrophages induced NMDA receptor mediated neurotoxicity *in vitro* by secreting glutamate. *Neurosci Lett* 1991;**133**:159−62.
119. Piani D, Spranger M, Frei K, Schaffner A, Fontana A. Macrophage-induced cytotoxicity of *N*-methyl-D-aspartate receptor positive neurons involves excitatory amino acids rather than reactive oxygen intermediates and cytokines. *Eur J Immunol* 1992;**22**:2429−36.
120. Wang R, Green DR. Metabolic checkpoints in activated T cells. *Nat Immunol* 2012;**13**:907−15.
121. Wang R, Dillon CP, Shi LZ, Milasta S, Carter R, Finkelstein D, et al. The transcription factor Myc controls metabolic reprogramming upon T lymphocyte activation. *Immunity* 2011;**35**:871−82.
122. Mackenzie B, Erickson JD. Sodium-coupled neutral amino acid (System N/A) transporters of the *SLC38* gene family. *Pflugers Arch* 2004;**447**:784−95.
123. Carr EL, Kelman A, Wu GS, Gopaul R, Senkevitch E, Aghvanyan A, et al. Glutamine uptake and metabolism are coordinately regulated by ERK/MAPK during T lymphocyte activation. *J Immunol* 2010;**185**:1037−44.
124. Utsunomiya−Tate N, Endou H, Kanai Y. Cloning and functional characterization of a system ASC-like Na^+-dependent neutral amino acid transporter. *J Biol Chem* 1996;**271**:14883−90.
125. Levring TB, Hansen AK, Nielsen BL, Kongsbak M, von Essen MR, Woetmann A, et al. Activated human $CD4^+$ T cells express transporters for both cysteine and cystine. *Sci Rep* 2012;**2**:266.
126. Xue H, Field CJ. New role of glutamate as an immunoregulator *via* glutamate receptors and transporters. *Front Biosci (Schol Ed)* 2011;**3**:1007−20.
127. Noda M, Nakanishi H, Akaike N. Glutamate release from microglia *via* glutamate transporter is enhanced by amyloid-beta peptide. *Neuroscience* 1999;**92**:1465−74.
128. Olney JW, Sharpe LG. Brain lesions in an infant rhesus monkey treated with monsodium glutamate. *Science* 1969;**166**:386−8.
129. Danbolt NC. Glutamate uptake. *Prog Neurobiol* 2001;**65**:1−105.
130. Grewer C, Rauen T. Electrogenic glutamate transporters in the CNS: molecular mechanism, pre-steady-state kinetics, and their impact on synaptic signaling. *J Membr Biol* 2005;**203**:1−20.
131. Zerangue N, Kavanaugh MP. Flux coupling in a neuronal glutamate transporter. *Nature* 1996;**383**:634−7.
132. Bannai S, Kitamura E. Role of proton dissociation in the transport of cystine and glutamate in human diploid fibroblasts in culture. *J Biol Chem* 1981;**256**:5770−2.
133. Sato H, Tamba M, Ishii T, Bannai S. Cloning and expression of a plasma membrane cystine/glutamate exchange transporter composed of two distinct proteins. *J Biol Chem* 1999;**274**:11455−8.
134. Bannai S. Exchange of cystine and glutamate across plasma membrane of human fibroblasts. *J Biol Chem* 1986;**261**:2256−63.
135. Bender AS, Reichelt W, Norenberg MD. Characterization of cystine uptake in cultured astrocytes. *Neurochem Int* 2000;**37**:269−76.
136. Bukowski DM, Deneke SM, Lawrence RA, Jenkinson SG. A non-inducible cystine transport system in rat alveolar type II cells. *Am J Physiol* 1995;**268**:L21−6.
137. Deneke SM, Fanburg BL. Regulation of cellular glutathione. *Am J Physiol* 1989;**257**:L163−73.
138. Brand A, Singer K, Koehl GE, Kolitzus M, Schoenhammer G, Thiel A, et al. LDHA-associated lactic acid production blunts tumor immunosurveillance by T and NK cells. *Cell Metabol* 2016;**24**:657−71.
139. Colegio OR, Chu NQ, Szabo AL, Chu T, Rhebergen AM, Jairam V, et al. Functional polarization of tumour-associated macrophages by tumour-derived lactic acid. *Nature* 2014;**513**:559−63.
140. Peng M, Yin N, Chhangawala S, Xu K, Leslie CS, Li MO. Aerobic glycolysis promotes T helper 1 cell differentiation through an epigenetic mechanism. *Science* 2016;**354**:481−4.
141. Halestrap AP. Monocarboxylic acid transport. *Comp Physiol* 2013;**3**:1611−43.
142. Doherty JR, Yang C, Scott KEN, Cameron MD, Fallahi M, Li W, et al. Blocking lactate export by inhibiting the Myc target MCT1 disables glycolysis and glutathione synthesis. *Cancer Res* 2014;**74**:908−20.
143. Srinivas SR, Gopal E, Zhuang L, Itagaki S, Martin PM, Fei YJ, et al. Cloning and functional identification of slc5a12 as a sodium-coupled low-affinity transporter for monocarboxylates (SMCT2). *Biochem J* 2005;**392**:655−64.
144. Haas R, Smith J, Rocher-Ros V, Nadkarni S, Montero-Melendez T, D'Acquisto F, et al. Lactate regulates metabolic and pro-inflammatory circuits in control of T cell migration and effector functions. *PLoS Biol* 2015;**13**:e1002202.
145. Hirschhaeuser F, Sattler UG, Mueller-Klieser W. Lactate: a metabolic key player in cancer. *Cancer Res* 2011;**71**:6921−5.
146. Fischer K, Hoffmann P, Voelkl S, Meidenbauer N, Ammer J, Edinger M, et al. Inhibitory effect of tumor cell-derived lactic acid on human T cells. *Blood* 2007;**109**:3812−9.
147. Vegran F, Boidot R, Michiels C, Sonveaux P, Feron O. Lactate influx through the endothelial cell monocarboxylate transporter MCT1 supports an NF-κB/IL-8 pathway that drives tumor angiogenesis. *Cancer Res* 2011;**71**:2550−60.
148. Leite TC, Coelho RG, Da Silva D, Coelho WS, Marinho-Carvalho MM, Sola-Penna M. Lactate downregulates the glycolytic

enzymes hexokinase and phosphofructokinase in diverse tissues from mice. *FEBS Lett* 2011;**585**:92−8.
149. Angelin A, Gil-de-Gómez L, Dahiya S, Jiao J, Guo L, Levine MH, et al. Foxp3 reprograms T cell metabolism to function in low-glucose, high-lactate environments. *Cell Metabol* 2017;**25**:1282−93.
150. Zhang W, Wang G, Xu ZG, Tu H, Hu F, Dai J, et al. Lactate is a aatural suppressor of RLR signaling by targeting MAVS. *Cell* 2019; **178**:176−89. e15.
151. Hahn EL, Halestrap AP, Gamelli RL. Expression of the lactate transporter MCT1 in macrophages. *Shock* 2000;**13**:253−60.
152. Moreira TJ, Pierre K, Maekawa F, Repond C, Cebere A, Liljequist S, et al. Enhanced cerebral expression of MCT1 and MCT2 in a rat ischemia model occurs in activated microglial cells. *J Cereb Blood Flow Metab* 2009;**29**:1273−83.
153. Tan Z, Xie N, Banerjee S, Cui H, Fu M, Thannickal VJ, et al. The monocarboxylate transporter 4 is required for glycolytic reprogramming and inflammatory response in macrophages. *J Biol Chem* 2015;**290**:46−55.
154. Bin BH, Seo J, Kim ST. Function, structure, and transport aspects of ZIP and ZnT zinc transporters in immune cells. *J Immunol Res* 2018; **2018**:9365747.
155. Nolin E, Gans S, Llamas L, Bandyopadhyay S, Brittain SM, Bernasconi-Elias P, et al. Discovery of a ZIP7 inhibitor from a Notch pathway screen. *Nat Chem Biol* 2019;**15**:179−88.
156. Anzilotti C, Swan DJ, Boisson B, Deobagkar-Lele M, Oliveira C, Chabosseau P, et al. An essential role for the Zn^{2+} transporter ZIP7 in B cell development. *Nat Immunol* 2019;**20**:350−61.
157. Gomes KFB, Semzezem C, Batista R, Fukui RT, Santos AS, Correia MR, et al. Importance of zinc transporter 8 autoantibody in the diagnosis of type 1 diabetes in Latin Americans. *Sci Rep* 2017;**7**: 207.
158. Wenzlau JM, Liu Y, Yu L, Moua O, Fowler KT, Rangasamy S, et al. A common nonsynonymous single nucleotide polymorphism in the *SLC30A8* gene determines ZnT8 autoantibody specificity in type 1 diabetes. *Diabetes* 2008;**57**:2693−7.
159. Mandt T, Song Y, Scharenberg AM, Sahni J. SLC41A1 Mg^{2+} transport is regulated *via* Mg^{2+}-dependent endosomal recycling through its N-terminal cytoplasmic domain. *Biochem J* 2011;**439**: 129−39.
160. Romani A, Scarpa A. Regulation of cell magnesium. *Arch Biochem Biophys* 1992;**298**:1−12.
161. Goytain A, Quamme GA. Functional characterization of the mouse solute carrier, SLC41A2. *Biochem Biophys Res Commun* 2005;**330**: 701−5.
162. Wu X, Huang W, Prasad PD, Seth P, Rajan DP, Leibach FH, et al. Functional characteristics and tissue distribution pattern of organic cation transporter 2 (OCTN2), an organic cation/carnitine transporter. *J Pharmacol Exp Ther* 1999;**290**:1482−92.
163. Ingoglia F, Visigalli R, Rotoli BM, Barilli A, Riccardi B, Puccini P, et al. Human macrophage differentiation induces OCTN2-mediated L-carnitine transport through stimulation of mTOR−STAT3 axis. *J Leukoc Biol* 2017;**101**:665−74.
164. Phillis JW, O'Regan MH, Song D. 5-(*N*-Ethyl-*N*-isopropyl)-amiloride inhibits amino acid release from the ischemic rat cerebral cortex: role of Na^+−H^+ exchange. *Brain Res* 1998;**812**:297−300.
165. Sedlyarov V, Eichner R, Girardi E, Essletzbichler P, Goldmann U, Nunes-Hasler P, et al. The bicarbonate transporter SLC4A7 plays a key role in macrophage phagosome acidification. *Cell Host Microbe* 2018;**23**:766−74.
166. Console L, Scalise M, Tonazzi A, Giangregorio N, Indiveri C. Characterization of Exosomal SLC22A5 (OCTN2) carnitine transporter. *Sci Rep* 2018;**8**:3758.
167. Loynes CA, Lee JA, Robertson AL, Steel MJG, Ellett F, Feng Y, et al. PGE_2 production at sites of tissue injury promotes an anti-inflammatory neutrophil phenotype and determines the outcome of inflammation resolution *in vivo*. *Sci Adv* 2018;**4**. eaar8320.
168. Xu YZ, Thuraisingam T, Kanagaratham C, Tao S, Radzioch D. c-Src kinase is involved in the tyrosine phosphorylation and activity of SLC11A1 in differentiating macrophages. *PLoS One* 2018;**13**: e0196230.
169. Forbes JR, Gros P. Divalent-metal transport by NRAMP proteins at the interface of host−pathogen interactions. *Trends Microbiol* 2001; **9**:397−403.
170. Searle S, Blackwell JM. Evidence for a functional repeat polymorphism in the promoter of the human *NRAMP1* gene that correlates with autoimmune *versus* infectious disease susceptibility. *J Med Genet* 1999;**36**:295−9.
171. Biegel A, Knutter I, Hartrodt B, Gebauer S, Theis S, Luckner P, et al. The renal type H^+/peptide symporter PEPT2: structure−affinity relationships. *Amino Acids* 2006;**31**:137−56.
172. Hu Y, Song F, Jiang H, Nunez G, Smith DE. SLC15A2 and SLC15A4 mediate the transport of bacterially derived Di/tripeptides to enhance the nucleotide-binding oligomerization domain-dependent immune response in mouse bone marrow-derived macrophages. *J Immunol* 2018;**201**:652−62.
173. Kobayashi T, Shimabukuro-Demoto S, Yoshida-Sugitani R, Furuyama-Tanaka K, Karyu H, Sugiura Y, et al. The histidine transporter SLC15A4 coordinates mTOR-dependent inflammatory responses and pathogenic antibody production. *Immunity* 2014;**41**:375−88.
174. Li M, Anderson GD, Phillips BR, Kong W, Shen DD, Wang J. Interactions of amoxicillin and cefaclor with human renal organic anion and peptide transporters. *Drug Metab Dispos* 2006;**34**:547−55.
175. Vallee BL, Falchuk KH. The biochemical basis of zinc physiology. *Physiol Rev* 1993;**73**:79−118.
176. Wang X, Gao H, Wu W, Xie E, Yu Y, He X, et al. The zinc transporter Slc39a5 controls glucose sensing and insulin secretion in pancreatic β-cells *via* Sirt1- and Pgc-1α-mediated regulation of Glut2. *Protein Cell* 2019;**10**:436−49.
177. Chu DS. Zinc: a small molecule with a big impact on sperm function. *PLoS Biol* 2018;**16**:e2006204.
178. Mayer LS, Uciechowski P, Meyer S, Schwerdtle T, Rink L, Haase H. Differential impact of zinc deficiency on phagocytosis, oxidative burst, and production of pro-inflammatory cytokines by human monocytes. *Metallomics* 2014;**6**:1288−95.
179. Campo CA, Wellinghausen N, Faber C, Fischer A, Rink L. Zinc inhibits the mixed lymphocyte culture. *Biol Trace Elem Res* 2001;**79**:15−22.
180. Huang L, Kirschke CP, Zhang Y, Yu YY. The ZIP7 gene (*Slc39a7*) encodes a zinc transporter involved in zinc homeostasis of the Golgi apparatus. *J Biol Chem* 2005;**280**:15456−63.
181. Taylor KM, Morgan HE, Johnson A, Nicholson RI. Structure−function analysis of HKE4, a member of the new LIV-1 subfamily of zinc transporters. *Biochem J* 2004;**377**:131−9.
182. Huber KL, Hardy JA. Mechanism of zinc-mediated inhibition of caspase-9. *Protein Sci* 2012;**21**:1056−65.
183. Perry DK, Smyth MJ, Stennicke HR, Salvesen GS, Duriez P, Poirier GG, et al. Zinc is a potent inhibitor of the apoptotic protease, caspase-3. A novel target for zinc in the inhibition of apoptosis. *J Biol Chem* 1997;**272**:18530−3.
184. Miyai T, Hojyo S, Ikawa T, Kawamura M, Irie T, Ogura H, et al. Zinc transporter SLC39A10/ZIP10 facilitates antiapoptotic signaling during early B-cell development. *Proc Natl Acad Sci U S A* 2014; **111**:11780−5.
185. Shrivastava P, Katagiri T, Ogimoto M, Mizuno K, Yakura H. Dynamic regulation of Src-family kinases by CD45 in B cells. *Blood* 2004;**103**:1425−32.
186. Seda V, Mraz M. B-cell receptor signalling and its crosstalk with other pathways in normal and malignant cells. *Eur J Haematol* 2015; **94**:193−205.
187. Woodruff G, Bouwkamp CG, de Vrij FM, Lovenberg T, Bonaventure P, Kushner SA, et al. The zinc transporter SLC39A7 (ZIP7) is essential for regulation of cytosolic zinc levels. *Mol Pharmacol* 2018;**94**:1092−100.
188. Hojyo S, Miyai T, Fujishiro H, Kawamura M, Yasuda T, Hijikata A, et al. Zinc transporter SLC39A10/ZIP10 controls humoral immunity by modulating B-cell receptor signal strength. *Proc Natl Acad Sci U S A* 2014;**111**:11786−91.

189. Gao H, Zhao L, Wang H, Xie E, Wang X, Wu Q, et al. Metal transporter Slc39a10 regulates susceptibility to inflammatory stimuli by controlling macrophage survival. *Proc Natl Acad Sci U S A* 2017;**114**:12940−5.
190. Golden MN, Jackson A, Golden B. Effect of zinc on thymus of recently malnourished children. *Lancet* 1977;**2**:1057−9.
191. King LE, Osati-Ashtiani F, Fraker PJ. Depletion of cells of the B lineage in the bone marrow of zinc-deficient mice. *Immunology* 1995;**85**:69−73.
192. Lee K, Sung C, Kim BG, Hahn JS. Activation of Aro80 transcription factor by heat-induced aromatic amino acid influx in *Saccharomyces cerevisiae*. *Biochem Biophys Res Commun* 2013;**438**:43−7.
193. Kitamura H, Morikawa H, Kamon H, Iguchi M, Hojyo S, Fukada T, et al. Toll-like receptor-mediated regulation of zinc homeostasis influences dendritic cell function. *Nat Immunol* 2006;**7**:971−7.
194. Liu MJ, Bao S, Gálvez-Peralta M, Pyle CJ, Rudawsky AC, Pavlovicz RE, et al. ZIP8 regulates host defense through zinc-mediated inhibition of NF-κB. *Cell Rep* 2013;**3**:386−400.
195. Sun H, Li C, Li S, Li X, Wang J, Zhou Z, et al. Gene silencing of ZnT8 attenuates inflammation and protects pancreatic tissue injury in T1D. *Immunol Lett* 2018;**198**:1−6.
196. Wenzlau JM, Juhl K, Yu L, Moua O, Sarkar SA, Gottlieb P, et al. The cation efflux transporter ZnT8 (Slc30A8) is a major autoantigen in human type 1 diabetes. *Proc Natl Acad Sci U S A* 2007;**104**:17040−5.
197. Nishida K, Hasegawa A, Nakae S, Oboki K, Saito H, Yamasaki S, et al. Zinc transporter Znt5/Slc30a5 is required for the mast cell-mediated delayed-type allergic reaction but not the immediate-type reaction. *J Exp Med* 2009;**206**:1351−64.
198. Feske S, Skolnik EY, Prakriya M. Ion channels and transporters in lymphocyte function and immunity. *Nat Rev Immunol* 2012;**12**:532.
199. Brandao K, Deason-Towne F, Perraud AL, Schmitz C. The role of Mg^{2+} in immune cells. *Immunol Res* 2013;**55**:261−9.
200. Sahni J, Scharenberg AM. The SLC41 family of MgtE-like magnesium transporters. *Mol Asp Med* 2013;**34**:620−8.
201. Tam M, Gomez S, Gonzalez-Gross M, Marcos A. Possible roles of magnesium on the immune system. *Eur J Clin Nutr* 2003;**57**:1193−7.
202. Galland L. Magnesium and immune function: an overview. *Magnesium* 1988;**7**:290−9.
203. Kolisek M, Nestler A, Vormann J, Schweigel-Rontgen M. Human gene *SLC41A1* encodes for the Na^+/Mg^{2+} exchanger. *Am J Physiol Cell Physiol* 2012;**302**:C318−26.
204. Sahni J, Nelson B, Scharenberg AM. *SLC41A2* encodes a plasma-membrane Mg^{2+} transporter. *Biochem J* 2007;**401**:505−13.
205. Koepsell H. The SLC22 family with transporters of organic cations, anions and zwitterions. *Mol Asp Med* 2013;**34**:413−35.
206. Srinivas SR, Prasad PD, Umapathy NS, Ganapathy V, Shekhawat PS. Transport of butyryl-L-carnitine, a potential prodrug, *via* the carnitine transporter OCTN2 and the amino acid transporter ATB(0,+). *Am J Physiol Gastrointest Liver Physiol* 2007;**293**:G1046−53.
207. Leung E, Hong J, Fraser AG, Merriman TR, Vishnu P, Krissansen GW. Polymorphisms in the organic cation transporter genes *SLC22A4* and *SLC22A5* and Crohn's disease in a New Zealand Caucasian cohort. *Immunol Cell Biol* 2006;**84**:233−6.
208. Fisher SA, Hampe J, Onnie CM, Daly MJ, Curley C, Purcell S, et al. Direct or indirect association in a complex disease: the role of SLC22A4 and SLC22A5 functional variants in Crohn disease. *Hum Mutat* 2006;**27**:778−85.
209. Peltekova VD, Wintle RF, Rubin LA, Amos CI, Huang Q, Gu X, et al. Functional variants of OCTN cation transporter genes are associated with Crohn disease. *Nat Genet* 2004;**36**:471−5.
210. Aalkjaer C, Boedtkjer E, Choi I, Lee S. Cation-coupled bicarbonate transporters. *Comp Physiol* 2014;**4**:1605−37.
211. Shimada H, Nakamura Y, Nakanishi T, Tamai I. OATP2A1/SLCO2A1-mediated prostaglandin E2 loading into intracellular acidic compartments of macrophages contributes to exocytotic secretion. *Biochem Pharmacol* 2015;**98**:629−38.
212. Skazik C, Heise R, Bostanci O, Paul N, Denecke B, Joussen S, et al. Differential expression of influx and efflux transport proteins in human antigen presenting cells. *Exp Dermatol* 2008;**17**:739−47.
213. Singh N, Gedda MR, Tiwari N, Singh SP, Bajpai S, Singh RK. Solute carrier protein family 11 member 1 (Slc11a1) activation efficiently inhibits *Leishmania donovani* survival in host macrophages. *J Parasit Dis* 2017;**41**:671−7.
214. Cellier MF, Courville P, Campion C. Nramp1 phagocyte intracellular metal withdrawal defense. *Microb Infect* 2007;**9**:1662−70.
215. Hedges JF, Kimmel E, Snyder DT, Jerome M, Jutila MA. Solute carrier 11A1 is expressed by innate lymphocytes and augments their activation. *J Immunol* 2013;**190**:4263−73.
216. Muangsombut V, Withatanung P, Srinon V, Chantratita N, Stevens MP, Blackwell JM, et al. *Burkholderia pseudomallei* evades Nramp1 (Slc11a1)- and NADPH oxidase-mediated killing in macrophages and exhibits Nramp1-dependent virulence gene expression. *Front Cell Infect Microbiol* 2017;**7**:350.
217. Nakamura N, Lill JR, Phung Q, Jiang Z, Bakalarski C, de Mazière A, et al. Endosomes are specialized platforms for bacterial sensing and NOD2 signalling. *Nature* 2014;**509**:240−4.
218. Charriere GM, Ip WE, Dejardin S, Boyer L, Sokolovska A, Cappillino MP, et al. Identification of *Drosophila* Yin and PEPT2 as evolutionarily conserved phagosome-associated muramyl dipeptide transporters. *J Biol Chem* 2010;**285**:20147−54.
219. Wolf AJ, Underhill DM. Peptidoglycan recognition by the innate immune system. *Nat Rev Immunol* 2018;**18**:243−54.
220. Sledzińska A, Hemmers S, Mair F, Gorka O, Ruland J, Fairbairn L, et al. TGF-β signalling is required for $CD4^+$ T cell homeostasis but dispensable for regulatory T cell function. *PLoS Biol* 2013;**11**:e1001674.
221. Galgani M, De Rosa V, Matarese G. T cell metabolism and susceptibility to autoimmune diseases. *Mol Immunol* 2015;**68**:558−63.
222. Mehta MM, Chandel NS. Targeting metabolism for lupus therapy. *Sci Transl Med* 2015;**7**:274fs5.
223. Murray CM, Hutchinson R, Bantick JR, Belfield GP, Benjamin AD, Brazma D, et al. Monocarboxylate transporter MCT1 is a target for immunosuppression. *Nat Chem Biol* 2005;**1**:371−6.
224. Li X, Wenes M, Romero P, Huang SC, Fendt SM, Ho PC. Navigating metabolic pathways to enhance antitumour immunity and immunotherapy. *Nat Rev Clin Oncol* 2019;**16**:425−41.
225. Cascone T, McKenzie JA, Mbofung RM, Punt S, Wang Z, Xu C, et al. Increased tumor glycolysis characterizes immune resistance to adoptive T cell therapy. *Cell Metabol* 2018;**27**:977−87.
226. Chen L, Chen XW, Huang X, Song BL, Wang Y, Wang Y. Regulation of glucose and lipid metabolism in health and disease. *Sci China Life Sci* 2019;**62**:1420−58.