Solute carrier transporters: the metabolic gatekeepers of immune cells

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Received 2 July 2019; received in revised form 29 September 2019; accepted 31 October 2019

**KEY WORDS**

Solute carrier; Lymphocytes;

**Abstract**

Solute carrier (SLC) transporters mediate 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...
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. 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. 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. Nonetheless, some SLC transporters function as bidirectional or even efflux transporters.

SLC transporters—largest transporter family consisting of 456 integral membrane proteins 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. 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.

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, kidneys, or even present in endocrine organs like adipose tissues. 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.

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. Therefore, immune cells are excellent models to study the functional outcomes of cellular metabolism, 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. Generally, the immune cells can be roughly divided into lymphoid and myeloid lineages.

Macrophages, key representative of myeloid lineages, represent an innate immune cell forming the first barrier that protects against invading pathogens. Two polarized types of macrophages have been recognized, named the classically activated (or M1) macrophages and the alternative activated (or M2) macrophages. Exposure to Toll-like receptor (TLR) ligand, with or without interferon-γ (IFN-γ), 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. 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. 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.

For another, T and B cells are two most vital components of lymphocyte lineages for the adaptive immune system. T or B cell deficiencies are shown to lead to severe immunodeficiencies. As such, the different stages of T cells are integrated with systemic inflammation and conducive to protecting the host from invading pathogens. T cells are divided into two functionally distinct lineages by the exclusive expression of the co-receptor CD4 or CD8. 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). Likewise, naïve CD8+ T cells proliferate and differentiate into cytotoxic effector cells to eliminate infected or malignant cells upon cognate antigen stimulation. And only a small portion of them eventually forms the memory population after rapid expansion and concomitant contraction. 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.

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. 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. 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. 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, 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. 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 describes thymocyte differentiation, as well as the identification of CD4⁺ and CD8⁺ T-cell subsets, memory T cells, and Tregs. 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, but upon activation, GLUT1 is immediately trafficked to the cell membrane and mediates glucose influx to accommodate the dramatic increase of metabolic demands (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 and infection with HIV-1 in vivo. 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. 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.

The differentiation of CD4⁺ T cells is now recognized as dynamic, and proinflammatory CD4⁺ T cells are able to re-differentiate 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). 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. Moreover, Tregs induce immune tolerance against allo-antigens and self-antigens.

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. 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. 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. 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.

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. When cytokines were withdrawn from hematopoietic cell lines, GLUT1 was internalized and returned back to the cell membrane upon renewed addition of IL-3. The phosphatidylinositol-3-OH kinase/serine-threonine kinase (PI-3K/AKT) pathway plays a vital role in IL-3-induced GLUT1 trafficking. 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. In addition, the metabolic checkpoint kinase complex mTORC1, cMYC, and estrogen related receptor alpha (ERRα) 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. 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. 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, while M2 polarized ones...
(in response to IL-4 and IL-13), mainly rely on mitochondrial oxidative metabolism\(^5\), with a lesser dependence on the anaerobic glycolytic pathway\(^6\).

It has been previously reported that GLUT1 is a critical regulator of glucose metabolism in macrophages\(^3\). When GLUT1 was overexpressed in macrophages, the glucose uptake and the expression of proinflammatory cytokines (TNF-\(\alpha\), IL-1\(\beta\), 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)\(^6\). 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\(^6\).

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\(^6\). Although metabolomics and in vitro analyses indicate 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 GLUT1+/+ ones\(^6\). While GLUT6 was previously reported to mediate glucose uptake in endometrial cancer cells\(^6\), 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\(^6\). The information reviewed above glucose transporters involved in immune cells are summarized in Table 1\(^6\).

### 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\(^1\). Glutamine is converted to glutamate by deamination and glutamate is then transformed to \(\alpha\)-ketoglutarate, which may feed into other metabolic pathways like the tricarboxylic acid (TCA) cycle and lipid synthesis\(^2\).

The expression of glutamine transporters and glutaminolysis components is increased in activated T cells through a MYC-dependent pathway\(^1\). 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 family contains transporters that mediate the entry of glutamine into cells\(^1\), 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\(^2\).
| 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$_{50} = \sim 68 \mu$mol/L), oxime derivatives (IC$_{50} = \sim 9$--$24 \mu$mol/L), EF24, WZB27 (IC$_{50} = \sim 5 \mu$mol/L), WZB115 (IC$_{50} = \sim 0.3 \mu$mol/L), WZB117 (IC$_{50} = \sim 10 \mu$mol/L), BAY 876 (IC$_{50} = \sim 2$ mmol/L), STF 31 (IC$_{50} = \sim 1 \mu$mol/L) | • GLUT1 is nearly undetectable in quiescent T cells.  
• Increased surface abundance of GLUT1 is observed in CD4$^+$ and CD8$^+$ T cells following TCR or infected with HIV-1.  
• CD4 Tefs 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. | Rs1385129 in SLC2A1 | 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$_{50} = \sim 1.67 \mu$mol/L), WZB117, cytochalasin B ($K_i = \sim 0.4 \mu$mol/L), phloretin, phlorizin | • GLUT3 has the potential to mediate GLUT1-independence glucose uptake in CD8$^+$ Tefs 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$_{50} = \sim 68 \mu$mol/L), BAY 876 (IC$_{50} = \sim 0.29 \mu$mol/L), WZB117, cytochalasin B (IC$_{50} = \sim 0.2 \mu$mol/L), phloretin (IC$_{50} = \sim 10 \mu$mol/L), phlorizin (IC$_{50} = \sim 140 \mu$mol/L) | • GLUT4 shows activation-dependent mRNA upregulation in human CD4$^+$ T cells. |             | --           |
| SLC2A6 | GLUT6   (originally named GLUT9) | Facilitated transporter, low affinity for glucose | Glucose | -- | • GLUT6 shows activation-dependent mRNA upregulation in human CD4$^+$ T cells. |             | --           |
| SLC38A1 | ATA1, GlutN, 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), t-theanine | • Activation of T cells with CD3 and CD28 induces SLC38A1 expression levels. |             | 80–85         |

(continued on next page)
| Gene   | Alias                      | Transport mechanism                          | Substrate                                                                 | Inhibitor/blocker                                                                 | Comment                                                                                                                                                                                                 | Polymorphism                                      | Ref.   |
|--------|----------------------------|---------------------------------------------|----------------------------------------------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|--------|
| SLC38A2| ATA2, KIAA1382, SAT2       | Sodium-coupled transporter, pH-sensitive transporter | histidine, serine, alanine, asparagine, cysteine, glutamine, glycine, histidine, methionine, proline, serine | N-Methyl-D-glucamine, choline, 2-methylaminoisobutyric acid \( (K_{m} = \sim 0.39 \text{ mmol/L}, \text{pH } 8.0) \) | • 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, \( \gamma \)-Glu-p-nitroanilide \( (IC_{50} = \sim 1000 \text{ \mu mol/L}), 1,2,3\)-dithiazoles \( (IC_{50} = \sim 3-30 \text{ \mu mol/L}), 2\)-substituted \( N\)-glutamylanilide \( (IC_{50} = \sim 1.3 \text{ \mu mol/L}), V-9302 \( (IC_{50} = \sim 9.6 \text{ \mu mol/L}) \) | • Rapid uptake of glutamine through SLC1A5 is triggered in TCR-stimulated naïve 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 \textit{ex vivo} cytokine responses to \textit{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-propanoic 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, pcuribenzenesulfonate | MCT1 internalizes lactate in human cytotoxic T lymphocytes (CTL) under high lactate condition.                                                                 | rs1049434 in SLC16A1, exhibits increased lactate transport \textit{via} SLA16A1 compared to the wild type Asp/A, seems to be 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-propanoic 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-\(\alpha\)- hydroxybutyrate | Ibuprofen \( (IC_{50} = 64 \text{ \mu mol/L}), \) fenoprofen \( (IC_{50} = 119 \text{ \mu mol/L}), \) ketoprofen \( (IC_{50} = 27 \text{ \mu mol/L}) \) | SLC5A12 senses high lactate concentrations upon entering inflammatory sites in CD4\(^{+}\) T cell subsets.                                                                 | —                                                 | 102    |
| SLC1A2 | EAAT2, GLT1               | X\(\text{AG}\)-sodium- and potassium- dependent transporter | \(\gamma\)-Glutamate \( (K_{m} = 391 \text{ \mu mol/L}), \) l- and \(\alpha\)-aspartate | WAY213613                                                                                | X\(\text{AG}\) regulates intracellular GSH store in monocyte-derived macrophages.                                                                 | —                                                 | 103–109 |
In addition, the SLC1A5 (alanine serine and cysteine transporter system 2, ASCT2) is also an important glutamine transporter whose expression levels are upregulated upon T cell activation. 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 mediate 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. 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), removing glutamate from extracellular space. 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. The second system Xc⁻/C0⁺ 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⁻/C0⁺ 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. It is a major way to provide cystine for glutathione and protein synthesis. The third system XAG is also Na⁺-independent and demonstrates an affinity for glutamine, cystine, and aspartate.

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. In human monocyte-derived macrophages, Xc⁻ and XAG systems are responsible for glutamate uptake. Extracellular glutamate increases intracellular GSH synthesis in these macrophages, suggesting that glutamate transporters may be involved in GSH synthesis regulation of macrophages. GSH synthesized from glutamate, cysteine, and glycine, is particularly important for immune cells in maintaining thiol redox state and protecting from oxidative stress.

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. Lactic acid is transported across biological membranes through four reversible monocarboxylate transporters (MCT) that belong to the SLC16 family of solute carriers comprising a total 14 members that share highly similar sequences.
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\(^ {143}\). Similarly, sodium-coupled lactate transport is also performed by the widely expressed high-affinity transporter SLC5A8 or the low-affinity transporter SLC5A12\(^ {145}\).

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)\(^ {159}\). 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\(^ {97–99,154–157}\).

#### 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 messenger 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\(^ {179}\). 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 and is upregulated, due to improved posttranscriptional processing via nicotinamide adenine dinucleotide phosphate (NADPH) into the cytosol\(^ {150,151}\) (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\(^ {160}\), 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 a blation in human osteosarcoma cell line MG-63 in a zinc-independent manner\(^ {157}\). 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 STATS, are
| Gene Alias | Transport mechanism | Substrate | Inhibitor/blocker | Comment | Polymorphism | Ref. |
|------------|---------------------|-----------|------------------|---------|--------------|-----|
| SLC39A7 ZIP7, Ke-4 | Inward-open and outward-open conformation changes | Zinc, manganese | NVS-ZIP7-4 (IC50 = 0.13 μmol/L) | • SLC39A7 is essential for the Zn2+ 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 | Zn2+/H+ exchanger | Zinc | — | ZnT8 acts as an immunogen in autoimmune diabetes in type I diabetes (T1D). | The type I 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+/Mg2+ co-transporter driving by electrochemical gradient of Na+ | Mg2+, Fe2+, Zn2+, Cu2+, Co2+, and Cd2+ | Amiloride (Ki = ~7 μmol/L), quinidine, or imipramine | SLC42A1 and SLC41A2 regulate Mg2+ homeostasis cooperated with other Mg2+ transporters and ion channels in the lymphocytes. | — | 159,160 |
| SLC41A2 SLC41A1-L1 | Putative Mg2+ channel | Mg2+, Ba2+, Ni2+, Co2+, Fe2+, and Mn2+ | Ca2+ (high concentration) | — | 161 |
| SLC22A5 OCTN2 | Na+/L-carnitine co-transporter | Acetyl-L-carnitine, L-carnitine | Cefepime, cefoselis, cephaloridine, emetine (IC50 = 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+/HCO3− co-transporter | Na+, HCO3− | 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 (pKf = ~5.4), bromsulphthalein (pKf = ~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 | Fe2+, Mn2+ 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. (continued on next page) | 168–170 |
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 (Fig. 2). In innate immunity, Slc39a10-deficiency 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. 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 Zn2+ 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.

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. 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. SLC39A8 (ZIP8) is highly induced in response to LPS and TNFα, leading to a rapid increase of intracellular zinc levels. 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. 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, is reported as a major autoantigen and a potential diagnostic marker for type 1 diabetes, that is detected in different populations at varying levels; while ZnT5, which is responsible for NF-κB-dependent cytokine production in mast cells, has been associated with the allergic response. 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. 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 Mg2+, ranges between 14 and 20 mmol/L, but is more typically...
within the range of 0.3–1.0 mmol/L. 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, Mg²⁺ is also required for the regulation of the immune system. During the immune response, magnesium acts as a co-factor for immunoglobulin synthesis, antibody-dependent cytosis, 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. Studies of the regulation of Mg²⁺ homeostasis proposed SLC41A1 and SLC41A2 as two key Mg²⁺ transporters. SLC41A1 is ubiquitously expressed in most tissues and lymphoid cell lines, and it functions as an Mg²⁺/Na⁺ exchanger, 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 Mg²⁺ permeable ion channels, like TRPM7 (transient receptor potential cation channel subfamily M member 7), in vertebrate DT-40 cells. This indicates that both SLC41A1 and SLC41A2 are significant players in regulating the Mg²⁺ 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. 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. Human SLC22A5 is a Na⁺/l-carnitine cotransporter which transports acetyl-l-carnitine and butyryl-l-carnitine as well, while human SLC22A4 is another l-carnitine transporter with lower affinity. The human genes encoding SLC22A5 and SLC22A4 are both located on chromosome 5q in a locus that is associated with many inflammatory diseases. Many studies suggest that carnitine transport deficiency might play a role in the pathogenesis of Crohn’s disease. 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 macropores during immune responses. CO₂ and HCO₃⁻ are general and pivotal components in the body’s buffering system. The maintenance of the intracellular level of HCO₃⁻ correlates with the intracellular pH. The electroneutral Na⁺/HCO₃⁻-cotransporter NBC1 coded by SLC4A7 is stimulated by CO₂/HCO₃⁻ transport associated with Na⁺. NBC1 transports the Na⁺ and HCO₃⁻ into the cytoplasm at the ratio of 1Na⁺:1HCO₃⁻. 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\textsuperscript{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\textsuperscript{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 vitro evidence is also needed.

7.3. The role of SLC20A1 in PEG2 exocytosis from macrophages

Prostaglandin E2 (PEG2), which is partially regulated by the transporter OATP2A1/SLC20A1, 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\textsuperscript{167}. Based on a deficient mouse model, OATP2A is definitely responsible for the partial PEG2 exocytosis from macrophages in inflammatory responses\textsuperscript{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 SLC20B1, SLC20A1, and SLC20A4 are expressed in monocytes and antigen-presenting cells, macrophages, and dendritic cells, among which SLC20B1 and SLC20A4 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\textsuperscript{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 1A (SLC11A1) is a proton/divalent cation antiporter that is recruited to the membrane of lysosomes upon the phagocytosis of parasites\textsuperscript{213}. This transporter exerts pleiotropic effects in the defense against parasites and other pathogens. The deprivation of divalent cations, like 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\textsuperscript{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\textsuperscript{215}. Moreover, the increased production of nitric oxide (NO), IL-12, and TNF-α correlates the enhanced expression of SLC11A1 in parasite-engulfing macrophages\textsuperscript{13}. The activation of SLC11A1 could also confer resistance against pathogens in the phagosomes mediated by iron-dependent NADPH oxidase activity and NO formation\textsuperscript{216}.

7.5. SLC15A2 and SLC15A4 in innate immunity against bacteria

Solute carrier family 15 (SLC15) members are H\textsuperscript{+}-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\textsuperscript{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\textsuperscript{72}. Transcription factors NF-κB and AP-1 are induced in the NOD signaling pathway, which in turn enhances the production of pro-inflammatory cytokines\textsuperscript{19}. SLC15A2 and SLC15A4 collaborate to import bacteria-derived ligands into the cytosol of macrophages, thereby enhancing the production of pro-inflammatory cytokines\textsuperscript{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)\textsuperscript{220,221}. Alteration of the glucose metabolism by inhibiting GLUT5s might be a promising strategy to reduce the proliferation and hyperactivation of autoreactive T cells in these autoimmune diseases\textsuperscript{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\textsuperscript{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)\textsuperscript{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\textsuperscript{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.

Acknowledgments

This research was supported by Nation Science and Technology Major Projects for Major New Drugs Innovation and Development (2018ZX09711003-004-002 to Ligong Chen, China), Ministry of Science and Technology of China National Key R&D Programs (2018YFA0506903 to Ligong Chen), National Natural Science Foundation of China grants (91857108 to Ligong Chen), Tsinghua University Initiative Scientific Research Program (20161080086 to Ligong Chen, China).

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.

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