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*J Immunol* 2006; 176:5918-5924;

doi: 10.4049/jimmunol.176.10.5918

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*The Journal of Immunology* is published twice each month by The American Association of Immunologists, Inc.,
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Print ISSN: 0022-1767 Online ISSN: 1550-6606.
Arginine Transport via Cationic Amino Acid Transporter 2 Plays a Critical Regulatory Role in Classical or Alternative Activation of Macrophages

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Arginine is processed by macrophages in response to the cytokines to which these cells are exposed. Th1-type cytokines induce NO synthase 2, which metabolizes arginine into nitrites, while the Th2-type cytokines produce arginase, which converts arginine into polyamines and proline. Activation of bone marrow-derived macrophages by these two types of cytokines increases L-arginine transport only through the γ⁺ system. Analysis of the expression of the genes involved in this system showed that Slc7a1, encoding cationic amino acid transporters (CAT), is constitutively expressed and is not modified by activating agents, while Slc7a2, encoding CAT2, is induced during both classical and alternative activation. Macrophages from Slc7a2 knockout mice showed a decrease in L-arginine transport in response to the two kinds of cytokines. However, while NO synthase 2 and arginase expression were unmodified in these cells, the catabolism of arginine was impaired by both pathways, producing smaller amounts of nitrites and also of polyamines and proline. In addition, the induction of Slc7a2 expression was independent of the arginine available and of the enzymes that metabolize it. In conclusion, the increased arginine transport mediated by activators is strongly regulated by CAT2 expression, which could limit the function of macrophages.


To perform their function, macrophages must be activated either by Th1-type cytokines, such as IFN-γ, which is called classical activation or M1, or by Th2-type cytokines, such as IL-4, IL-10, IL-13, etc., referred to as alternative activation or M2 (1). Activation induces biochemical and morphological modifications in the macrophages that allow them to perform their functional activity (2). Activation blocks the proliferation of these cells (3). The two types of activation are characterized by the way in which arginine is processed. Th1-type cytokines induce NO synthase (NOS), causing the production of NO, while Th2-type cytokines produce arginase, which metabolizes arginine in polyamines and triggers the urea pathway (4, 5).

Cell activation requires arginine for the synthesis of proteins, for the production of NO via classical activation, and for the production of polyamines and proline through alternative activation (1, 5). The extracellular milieu is the main source of arginine. The functional significance of arginine transporters was demonstrated in macrophages, in which NOS2-mediated NO synthesis largely depends on the extracellular supply of L-arginine (6–8). Arginine crosses the plasma membrane through several transport systems. Depending on the cell type, a number of transport activities may be induced (9). The Slc7a7 family of transporters is divided into two subgroups, the cationic amino acid (the cationic amino acid transporter (CAT) family, Slc7a1–4) and the glycophosphoinositol-associated amino acid transporters (the gpaAT family, Slc7a5–11), also called L chains or catalytic chains of the hetero(d)meric amino acid transporters. The CAT family includes four members, CAT-1 to CAT-4, whose corresponding genes are Slc7a1 to Slc7a4. The first three members transport cationic L-amino acids, while the function of CAT-4 is not known. The hetero(d)meric amino acid transporter family comprises seven proteins, whose genes are Slc7a5 to Slc7a11; however, only γ⁺LAT2 (Slc7a6), γ⁺LAT1 (Slc7a7), and δ⁺γ⁺AT (Slc7a9) transport cationic amino acids (9). In addition, the B⁰⁺γ⁺AT transporter (Slc6a14), belonging to the Slc6 family, also transports arginine, but in a sodium- and chloride-dependent fashion (10).

Macrophages require arginine to elaborate gene products when they become activated, e.g., IFN-γ induces the expression of >300 genes (11). Consequently, to meet their metabolic demands, macrophages require the uptake of exogenous arginine; this process may therefore be a key regulatory step for physiological responses in these cells. In this study, we investigated how classical and alternative activation affects arginine transport activity. To this end, we used bone marrow-derived macrophages, which are non-transformed cells that respond to both Th1- and Th2-type activating stimuli. We showed that macrophage activation leads to an increase in arginine transport. For both types of activation, the only gene to show increased expression was Slc7a2, the product of...
which is a limiting factor that regulates the catabolism of arginine and the production of NO and polyamines.

**Materials and Methods**

### Reagents

LPS and recombinant cytokines were purchased from Sigma-Aldrich. N'-hydroxy-nor-arg-amine (nor-NOHA) was purchased from Bachem. In several experiments, the results obtained with commercial LPS were compared with highly purified LPS from *Salmonella abortus equi*, donated by C. Galanos (Max Planck Institute, Freiburg, Germany) (12), and no differences were found. All other chemicals were of the highest purity grade available and were purchased from Sigma-Aldrich. Deionized water that had been further purified with a Millipore Milli-Q system was used.

### Cell culture

Bone marrow-derived macrophages as well as peritoneal macrophages were isolated from 6-wk-old BALB/c mice (Charles River Laboratories), as previously described (13). Bone marrow-derived macrophages were cultured in plastic tissue culture dishes (150 mm) in 40 ml of DMEM containing 20% FBS (Sigma-Aldrich) and 30% L cell-conditioned medium as a source of M-CSF. Penicillin and streptomycin were added. Cells were incubated at 37°C in a humidified 5% CO2 atmosphere. After 7 days of culture, macrophages were obtained as a homogenous population of adherent cells (>99% Mac-1+). To render cells quiescent, at 80% confluency, cells were deprived of L cell-conditioned medium for 16–18 h before treatment. Macrophages from knockout (KO) mice and the corresponding wild-type controls were isolated under the same conditions. The KO for *Slc7A2* has been reported (14), while the NOP2 KO mice were purchased from The Jackson Laboratory. Peritoneal exudate cells were harvested by lavage from mice that had been injected i.p. with 3 ml of 10% protease peptone (Difco Laboratories) 3 days earlier. Macrophage monolayers were prepared by seeding the exudate cell suspension into flat-bottom tissue culture plates. The cells were adhered for 2 h at 37°C, and the plates were washed vigorously to remove nonadherent cells. Animal experiments were performed in accordance with institutional and government guidelines (University of Barcelona).

### Quantitative RT-PCR analysis

Cells were washed twice with cold PBS, and total RNA was extracted with the acidic guanidinium thiocyanate-phenol-chloroform method, as described (15). RNA was treated with DNase (Ambion) to eliminate DNA contamination. For cDNA synthesis, 1 g of RNA and TaqMan reverse transcription reagents (including Multiscribe reverse transcriptase and random hexamers) were used, following the manufacturer’s instructions (Applied Biosystems). The primers used to amplify mouse were: for *Nop2*, GCCACCAAAACTTGCCAGAA and CGTACCAGGATGCTTGAATT; for *arginase 1*, AACAGCCGACGTTGATTTAAC and GGTTTTCATGTCGGAATC; for *Slc7A1*, CGTGCAGCAGTGGCAGAGC and TGACCTCAGGACCAGTTGCGA; for *Slc7A2*, GTGAAAGGTTGCGAATCCACA and CGTTAAAACGTCGACA; and for *Slc7A3*, GGCTCTTCTGCGCATTCT and TAGCAAGGACACGGAACA. Real-time monitoring of PCR amplification of cDNAs was done using the TaqMan Universal master mix (Applied Biosystems) in an ABI Prism 7700 sequence Detection System (Applied Biosystems). Relative quantification of gene expression was performed using β-actin, as described in the ‘TaqMan users’ manual (GCACCAACCTTCTCAACAT GACCTGT and CTGCTGGAAGTCTTAGGCAACACATA). The threshold cycle was defined as the cycle number at which the fluorescence corresponding to the amplified PCR product is detected. The PCR arbitrary units of each gene were defined as the mRNA levels normalized to the β actin expression level in each sample. The RT-PCR analysis was controlled by sequencing the amplification products. In addition, we included a sample without RNA in each reaction.

### Transport measurements

Cells were plated in 6-well plates 1–2 days before the transport assay (10⁶ cells/well) and treated as indicated in the figures. To measure t-arginine uptake, cells were washed three times in preheated (37°C) uptake solution (10 mM HEPES, 5.4 mM KCl, 1.2 mM MgSO₄, 7 mM H₂O, 2.8 mM CaCl₂, 2 mM H₂O, 1 mM KH₂PO₄, and 137 mM NaCl (pH 7.4)). They were then incubated with 0.5 ml of uptake solution containing 50 μM l-[H]arginine (5 μCi/ml) in the presence or absence of t-leucine (5 mM) or t-arginine (10 mM) for 1 min. Uptake was stopped by removing the uptake solution and washing cells with 2 ml of ice-cold stop solution (10 mM HEPES, 10 mM Tris, and 137 mM NaCl (pH 7.4) with 10 mM nonradioactive t-arg-amine) three times. After the third wash, cells were lysed in 200 μl of 0.1% SDS and 100 mM NaOH, and 100 μl was used to measure the radioactivity associated with the cells. Values obtained in the presence of 5 mM t-arginine as competitor were always below 10% of the total transport and were subtracted to estimate γ’ activity.

### Catabolism of l-arginine in macrophages

Macrophages were incubated with a number of cytokines in a microplate (10⁶ cells/well). After 24 h, cells were washed and incubated for 2 or 6 h at 37°C in 0.1 ml of arginine-free DMEM containing 2% FCS and 0.1 μCi of l-([U-14C]) arginine (Amersham Biosciences). Cells were subsequently lysed by two freeze-thaw cycles. The remaining arginine and synthesis of metabolic products were evaluated by TLC. To identify the spots, 10 μl of a solution containing 25 mg/ml arginine, ornithine, and spermine was added to the cell lysates. A total of 20 μl of the samples was spotted onto TLC plates (Cromatoplates TLC 20 x 20 cm; Silica Gel 60 F254; Merck) and dried for 1 h at 42°C. Plates were developed in the solvent system chloroform/methanol/ammonium hydroxide/water 0.5/4.5/2.0/1.0 (v/v/v) and dried. Spots were developed with ninhydrin (Spray Solution; Merck) by heating at 120°C for 5 min and scraped into scintillation tubes containing 6 ml of EcoscintA (National Diagnostics). Radioactivity was determined by scintillation counting (Beckman Instruments), and the values for each compound were expressed as percentage of the total radioactivity measured in triplicate cultures ± SD.

### Nitrite production and arginase activity

NO was measured as nitrite using the Griess reagent (16). Culture supernatant was mixed with 100 μl of 1% sulfanilamide, 0.1% N-(1-naphthyl)-ethylendiamine dihydrochloride, and 2.5% H₃PO₄. Absorbance was measured at 540 nm in a microplate reader (Molecular Devices). Arginase activity was measured in cell lysates, as previously described (16), but with slight modifications. Briefly, cells were lysed with 100 μl of 0.1% Triton X-100. After 30 min on a shaker, 100 μl of 25 mM Tris-HCl was added. We then added 10 μl of 10 mM MnCl₂ to 100 μl of this lysate, and the enzyme was activated by heating for 10 min at 56°C. Arginine hydrolysis was conducted by incubating the lysate with 100 μl of 0.5 M l-arginine (pH 9.7) at 37°C for 15–120 min. The reaction was stopped by adding 1 ml of 50% H₃SO₄ (96%)/H₃PO₄ (85%)/H₂O₂ (1/3/7, v/v/v). The urea concentration was measured at 540 nm after addition of 40 ml of α-isonitrosopropiophene (dissolved in 100% ethanol), followed by heating at 95°C for 30 min. One unit of enzyme activity was defined as the amount of enzyme that catalyzes the formation of 1 μmol of urea per minute.

### Statistical analysis

To calculate the statistical differences between the control and treated samples, we used the Student’s paired t test. Values of p < 0.05 or lower were considered significant.

### Results

#### M1 and M2 activation catalyzes arginase activity differently

In our experiments, we used bone marrow-derived macrophages, a homogeneous population of primary and quiescent cells. Treatment of these cells with several cytokines causes a series of modifications that allow them to develop their functional activities (3). To study M1 activation, we used IFN-γ or LPS, while IL-4 and IL-10 were used to examine M2 activation. Although these two types of activation regulate distinct sets of genes (17), both require arginine, either for NO production in classical activation or as a substrate for arginase induced during alternative activation. Only molecules from M1 activation induced nitrite production, while only cytokines involved in M2 activation stimulated arginase activity (Fig. 1, A and B). IFN-γ and LPS, but not IL-4 or IL-10, led to NOS expression. In contrast, Th2-type but not Th1-type cytokines induced arginase (Fig. 1, A and B). To determine the metabolism of arginine, we incubated activated macrophages with radiolabeled substrate and then separated the distinct products by TLC. When macrophages were incubated with Th2-type cytokines, an increased amount of ornithine and spermine were produced as a result of the catabolic activity of arginase (Fig. 1C). However, when these cells were treated with IFN-γ or LPS, the

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M1 and M2 activation increases arginine transport through the y⁺ system, thereby inducing Slc7A2 expression

Because arginine is required for macrophage metabolism, in this study we examined whether M1 and M2 activation modulates the transport of this amino acid. In a dose-dependent manner, both LPS and IL-4 produced an increase in arginine transport (Fig. 1D). Next, among the transport systems that mediate arginine uptake (y⁺, B⁺, b⁺, and y⁻L) (9), we identified the system induced in macrophages activated by Th1- or Th2-type cytokines. Arginine transport was measured in the absence and in the presence of 5 mM l-leucine, in medium containing sodium, to distinguish between total and y⁺ system-mediated transport. l-leucine inhibited most of the basal l-arginine transport, indicating that very little y⁺ activity is present in these macrophages under basal conditions. In contrast, the increase in transport that occurred in the presence of Th1- or Th2-type cytokines was mediated by the y⁺ system (Fig. 1E).

The y⁺ system is encoded by the CAT genes Slc7A1 (19, 20), Slc7A2 (21, 22), and Slc7A3 (23). Using a quantitative PCR, we determined the levels of the three members of the y⁺ system in macrophages activated by Th1- and Th2-type cytokines. Low levels of Slc7A1 were found in untreated cells. Expression of this gene was not modified by the treatments (Fig. 2), Slc7A2 was not detected in quiescent cells, but was induced by LPS and LPS +
IFN-γ and also by IL-4 and IL-4 + IL-10. Slc7A3 was not detected. In addition, the expression of the genes of the γ + system was measured in arginine-free medium; however, no differences in induction by the distinct cytokines were observed in relation to the controls (Fig. 2).

Our results to date indicate that, in basal conditions, CAT1 mediates the transport of arginine through the γ + system, while CAT2 is the main t-arginine transporter for activated macrophages. To confirm these data, we used macrophages from mice with disrupted Slc7A2 (14). In basal conditions, without stimulation, the amount of arginine transported was similar in macrophages from Slc7A2 KO mice and controls (Fig. 3A). However, while classical or alternative activators produced an increase in arginine transport in controls, no increase in cells from Slc7A2 KO mice was observed (Fig. 3A). When analyzed in more detail, the increased transport activity corresponded to the γ + system (data not shown). Slc7A1 expression was not modified in Slc7A2 KO macrophages or in controls when they were treated with activators, and Slc7A3 was not expressed in this model (data not shown). These results confirm that macrophage activation induces Slc7A2 expression, which is responsible for increased arginine transport.

In the absence of Slc7A2, macrophage activation is limited

We next addressed the functional consequences of Slc7A2 disruption on macrophages. M1 activation produced NO32, and M2 activation induced arginase 1 in Slc7A2 KO and control cells at similar levels (Fig. 3B). Comparable results were found when we measured the expression of protein by Western blot and when we used peritoneal macrophages (data not shown). When macrophages were incubated with activating agents, Slc7A2 KO macrophages showed a reduced catabolism of arginine (Fig. 4A). Also, the amounts of ornithine, spermine, and citrulline produced by these cells were decreased in relation to controls (Fig. 4B).

On the basis of the decreased catabolism of arginine in macrophages from Slc7A2 KO mice, we next studied the functional activity of these cells. Although the amounts of NOS2 were similar to those of controls, a significant decrease in NO production was detected in both bone marrow-derived and peritoneal macrophages (Fig. 4B). As the measurement of NO production is made with the entire cell, we conclude that the low amount of NO produced is due to the lower amount of intracellular arginine available. The enzymatic assay for arginase activity requires the rupture of the cell and the addition of external substrate. Under these conditions, arginase activity in Slc7A2 KO macrophages was similar to the controls. However, because the metabolic conversion of arginine into ornithine and polyamines is impaired in the entire cell, these data show that the amount of arginine available is the limiting factor for arginase activity. Therefore, CAT2 limits the activation of macrophages by Th1- and Th2-type cytokines.

Arginine transport is not regulated by the levels of NOS2 or arginase

We next studied whether the induction of the enzymes that catalyze arginine produces an increase in the transport of this amino acid. To explore the role of arginase 1, we used the specific inhibitor nor-NOHA, which blocks arginase activity by inhibiting the degradation of arginine into ornithine, but does not block the production of NO after IFN-γ treatment. Treatment with nor-NOHA did not affect the transport of arginine induced by the IL-4 + IL-10 or LPS + IFN-γ treatments (Fig. 5A). As expected, the induction of Slc7A2 expression in macrophages via classical and alternative activators produced a decrease in arginine transport (Fig. 5B). The expression of Slc7A3 was not modified, which is consistent with the decreased catabolism of arginine observed in the Slc7A2 KO macrophages (Fig. 4A).

Our results demonstrate a role for Slc7A2 in arginine transport and a limited role for CAT2 in arginine catabolism in macrophages. The ability of arginase 1 to be induced in macrophages suggests that this enzyme might be involved in the regulation of arginine transport, but this was not confirmed in the experiments described here. Further studies are needed to elucidate the role of arginase 1 in arginine transport in macrophages.

**FIGURE 3.** The induction of arginine transport by M1 and M2 activators is due to CAT2. A. Arginine uptake was measured in macrophages from Slc7A2 KO mice (■) and the corresponding wild-type controls (□). There is a significant difference for the amount of transport between the controls and KO macrophages after treatment with LPS, LPS + IFN-γ, IL-4, or IL-4 + IL-10 (p < 0.01). No significant differences were observed when we compared the corresponding values of the controls. Results are representative of two independent experiments. B. Macrophages from Slc7A2 KO mice (■) and the corresponding wild-type controls (□) were incubated with the activators indicated for 24 h, and the expression of NOS2 or arginase 1 was measured using real-time PCR. No significant differences were found between the corresponding values. Results are representative of two independent experiments.

**FIGURE 4.** CAT2 is a limiting factor for M1 and M2 activation. A. Macrophages from controls (□) and Slc7A2 KO mice (■) were incubated for 6 h with radiolabeled arginine. The products were then separated by TLC. Results are indicated as percentage of the arginine added at the beginning of the assay. The values shown correspond to the mean ± SD of three independent experiments. For arginine, ornithine, and spermine, in macrophages treated with IL-4 and IL-4 + IL-10, the values between controls and Slc7A2 KO macrophages were significantly different (p < 0.01). Also, for arginine and citrulline, values were significantly different after treatment with IFN-γ, LPS, or IFN-γ + LPS (p < 0.01). B. Macrophages from Slc7A2 KO mice and the corresponding wild-type controls were incubated for 24 h with the activators indicated, and the activity was measured. Citrulline was determined, and a significant decrease (p < 0.01) was found between the corresponding values for IFN-γ, LPS, and LPS + IFN-γ. Results are representative of three independent experiments.

**FIGURE 5.** Slc7A2 is required for the arginine transport induced by M1 and M2 activators. A. Macrophages from controls (□) and Slc7A2 KO mice (■) were incubated for 24 h with nor-NOHA, which blocks arginase activity by inhibiting the degradation of arginine into ornithine, but does not block the production of NO after IFN-γ treatment. Treatment with nor-NOHA did not affect the transport of arginine induced by the IL-4 + IL-10 or LPS + IFN-γ treatments (Fig. 5A). As expected, the induction of Slc7A2 expression in macrophages via classical and alternative activators produced a decrease in arginine transport (Fig. 5B). The expression of Slc7A3 was not modified, which is consistent with the decreased catabolism of arginine observed in the Slc7A2 KO macrophages (Fig. 4A).
alternative activation was not modified by incubation with nor-NOHA (Fig. 5B).

To determine the role of NOS2, we used macrophages from NOS2 KO mice. As in the case of arginase, the elimination of NOS2 did not modify the increase in arginine transport induced by M1 and M2 activators (Fig. 5C). No significant difference in Slc7A2 expression was observed when we compared NOS2 KO macrophages with the controls (Fig. 5D).

Discussion

Arginine is one of the metabolic and signaling functions required for protein synthesis by macrophages. In addition, it is the key amino acid involved in both M1 and M2 activation (1, 5). Macrophages require exogenous arginine to meet their metabolic demands. Therefore, the transport of this amino acid across the plasma membrane is an essential regulatory first step during activation of the macrophage, which synthesizes a large number of proteins (11). In addition, these cells catabolize arginine to NO by NOS2 induced by Th1-type cytokines or to ornithine, proline, and polyamines by arginase induced by the Th2-type cytokines (1, 5, 24).

Stimulation of l-arginine transport by only Th1-type inducers has been reported in several macrophage populations, including murine peritoneal (14, 25–27), rat alveolar (28), human monocyte derived (27), and the murine cell lines J774 (27, 29–31) and RAW264 (32). However, data on arginine transport in macrophages require exogenous arginine to meet their metabolic demands. Therefore, the transport of this amino acid across the plasma membrane is an essential regulatory first step during activation of the macrophage, which synthesizes a large number of proteins (11). In addition, these cells catabolize arginine to NO by NOS2 induced by Th1-type cytokines or to ornithine, proline, and polyamines by arginase induced by the Th2-type cytokines (1, 5, 24).

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FIGURE 5. Arginine uptake and Slc7A2 induction are independent of arginase or NOS2 activity. A, Macrophages were incubated for 2 h with or without nor-NOHA (50 μM), and the activators indicated were then added and macrophages were incubated for 24 h. Arginine uptake was then measured. B, Slc7A1, Slc7A2, and Slc7A3 expression was determined by real-time PCR under the same conditions as A. For arginine transport and gene expression, no significant differences were found between cells treated or not with nor-NOHA. C, Macrophages from NOS2 KO mice and wild-type controls were incubated for 24 h with the activators indicated. Arginine uptake was then measured. D, Slc7A1, Slc7A2, and Slc7A3 expression was determined by real-time PCR under the same conditions as C. For arginine transport and gene expression, no significant differences were found between cells from NOS2 KO mice and the controls. Results are representative of three independent experiments.
(C57BL/6 or BALB/c) do not explain these discrepancies because similar results were found when we used the two strains (data not shown). It should be noted that for these authors, the production of NO in fibroblasts and astrocytes is not completely dependent on CAT2 (35, 36).

Recently, we reported that the transport system for nucleosides in macrophages differs when cells proliferate or when they become activated by either IFN-γ or LPS (37, 38). This finding indicates distinct pools for different activities. When we studied the effect of M-CSF on arginine transport, no increase was observed in relation to the controls and no expression of Slc7A2 was detected (39). This observation shows that the arginine transport systems used in macrophages differ when these cells are activated or when they proliferate. Therefore, the regulation of Slc7A2 is a limiting factor for the activation of macrophages by restricting the supply of the substrate to the appropriate machinery that triggers M1 or M2 activation.

Regarding the control of arginine transport by NOS2, there are contradictory data in the literature. Although some studies report that the LPS-induced NOS2 expression regulates arginine transport (27, 40), in other cases, the regulation of this transport is independent of NOS2 activity (30). These differences may be related to the distinct populations of macrophages used in the studies, as well as to the methods applied to inhibit NOS2 activity. Using macrophages from NOS2 KO animals, we found that M1 and M2 activators induce Slc7A2 expression, which is responsible for the increase in l-arginine transport. Furthermore, no modifications of Slc7A2 expression or transport induced by activators were detected when we blocked arginase activity, thus demonstrating that the activators’ control over Slc7A2 is independent of the induction of either NOS2 or arginase activity. However, several signal transduction pathways may be common for the regulation of NOS2 and Slc7A2 genes, such as NF-κB (41).

The catabolism of arginine by macrophages through NOS2 or arginase generates several crucial products for immune regulation. For example, NOS2 produces NO, while arginase gives proline and polyamines, thereby inducing the synthesis of fibrinogen, which plays a role in inflammation (42). However, in some cases, the degradation products of arginine have a beneficial effect on intracellular microbes. For example, polyamines are required for the intracellular growth of Leishmania (24). Also, Mycobacterium enriches arginine transport in infected macrophages and acquires the metabolites necessary for bacterial growth (43). Furthermore, polyamines modulate the functional activities of macrophages (44). For example, spermine inhibits proinflammatory cytokine synthesis (45–48) and has been reported to down-regulate arginine transport and NOS2 expression in rat alveolar macrophages (49).

Several of the genes involved in the control of growth or amino acid metabolism are regulated by amino acid availability (50). In our studies, in the absence of arginine, no differences were found for the induction of genes regulated by M1 (MHC class II IA-β, NOS2, or TNF-α) or M2 activators (arginase 1 or mannose receptor). In addition, the absence of arginine did not affect the regulation of the transporter genes Slc7A1 or Slc7A2.

In conclusion, there is a clear association between CAT2 and macrophage activation. This finding is of particular interest because arginine transporters may offer a suitable new drug target for the clinical management of aberrant macrophage activation in diseases.

Acknowledgments
We thank Tanya Yates for editing the manuscript.

Disclosures
The authors have no financial conflict of interest.

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