Metal transporter Slc39a10 regulates susceptibility to inflammatory stimuli by controlling macrophage survival

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Zn plays a key role in controlling macrophage function during an inflammatory event. Cellular Zn homeostasis is regulated by two families of metal transporters, the SLC39A family of importers and the SLC30A family of exporters; however, the precise role of these transporters in maintaining macrophage function is poorly understood. Using macrophage-specific Slc39a10-knockout (Slc39a10–/–; LysM-Cre+) mice, we found that Slc39a10 plays an essential role in macrophage survival by mediating Zn homeostasis in response to LPS stimulation. Compared with Slc39a10+/+ mice, Slc39a10–/–; LysM-Cre+ mice had significantly lower mortality following LPS stimulation as well as reduced liver damage and lower levels of circulating inflammatory cytokines. Moreover, reduced intracellular Zn concentration in Slc39a10–/–; LysM-Cre+ macrophages led to the stabilization of p53, which increased apoptosis upon LPS stimulation. Concomitant knock-out of p53 largely reversed the phenotype of Slc39a10–/–; LysM-Cre+ mice. Finally, the phenotype in Slc39a10–/–; LysM-Cre+ mice was mimicked in wild-type mice using the Zn chelator TPEN and was reversed with Zn supplementation. Taken together, these results suggest that Slc39a10 plays a role in promoting the survival of macrophages through a Zn/p53-dependent axis in response to inflammatory stimuli.

SLC39A10 | zinc | macrophage | ZIP10 | inflammation

Macrophages play a critical role in innate immunity through three major functions: phagocytosis, antigen presentation, and immunomodulation (1). Interestingly, Zn was recently linked to antimicrobial responses in macrophages (2). In a mouse model of polymicrobial sepsis, Zn supplementation increased the phagocytic capacity of peritoneal macrophages (PMs) for Escherichia coli and Staphylococcus aureus (3). On the other hand, Zn chelation restricted the growth of specific pathogens such as Histoplasma capsulatum (4). In addition, LPS from Gram-negative bacteria reduced intracellular Zn concentrations in mouse dendritic cells, affecting their maturation (5). These findings indicate that Zn homeostasis in macrophages plays an active role in the antimicrobial response.

In mammals, multiple members of the solute-linked carrier 39 (SLC39A, or ZIP) and solute-linked carrier 30 (SLC30A, or ZnT) metal transporter families are essential for the regulation of Zn homeostasis (6–8). Several lines of evidence suggest that some SLC39A/SLC30A transporters are essential for the regulation of Zn homeostasis by regulating intracellular Zn levels; these include Slc39a6 (9), Slc39a10 (7, 8), Slc39a8 (10), and Slc30a5 (11). In human macrophages, LPS up-regulates the expression of Slc39a8, which promotes Zn uptake and negatively regulates proinflammatory responses by inhibiting IKKβ (12) and IL-10 (13). Interestingly, both Slc39a8 and Slc39a14 were recently associated with Mn transport (14–16). Thus, SLC39A and SLC30A transporters may play a role in the inflammatory response by mediating the homeostasis of Zn and/or other metals.

Despite evidence suggesting a link between SLC39A/SLC30A transporters and macrophage function, precisely how these transporters regulate this function remains poorly understood. Here, we systematically measured the expression of Slc39a9 and Slc30a transporters in mouse bone marrow-derived macrophages (BMDMs) following LPS stimulation. We found that the expression of Slc39a10 was significantly decreased following LPS stimulation. By generating and functionally characterizing macrophage-specific Slc39a10-knockout (Slc39a10–/–; LysM-Cre+) mice, we found that loss of Slc39a10 specifically reduces intracellular Zn and increases apoptosis in macrophages in response to inflammatory stimuli.

**Results**

**SLC39A10 Is Down-Regulated in Macrophages in Response to LPS Stimulation.** First, we mined a previously published dataset of 106 patients with sepsis (Gene Expression Omnibus dataset GSE51167, received for review May 25, 2017). In this dataset, Slc39a10 expression was significantly decreased following LPS stimulation. By p53 (4). In addition, LPS from Gram-negative bacteria restricted the growth of specific pathogens such as Histoplasma capsulatum (3). On the other hand, Zn chelation affected their maturation (5). These findings indicate that Zn transporter Slc39a10 regulates susceptibility to inflammatory stimuli by controlling macrophage survival

**Significance**

Zn is essential for maintaining the integrity of the immune system, and Zn homeostasis is tightly regulated by two families of ion transporters, SLC39A and SLC30A. Worldwide, an estimated two billion people have Zn deficiency, a condition that can impair immune function and increase susceptibility to a variety of infections. Despite their important roles in health and disease, the molecular mechanisms that underlie Zn transport and Zn homeostasis in macrophages are poorly understood. Here, we report that SLC39A10 plays an essential role in Zn homeostasis in macrophages, regulating the immune response following inflammatory stimuli. Specifically, we identified a role for SLC39A10 in regulating the survival of macrophages via a Zn/p53-dependent axis during the inflammatory response.

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GSE63042) (17) and compared the expression levels of SLC39A and SLC30A family members in peripheral blood cells of sepsis survivors (n = 78) and nonsurvivors (n = 28). As shown in Fig. 1 A and B, the expression of six transporters in the SLC39A9 family were significantly decreased in sepsis survivors compared with nonsurvivors, with SLC39A10 having the greatest reduction (0.519-fold difference). These results suggest that in humans SLC39A10 may play a role in regulating the host response in sepsis and subsequent complications.

Next, we measured the expression levels of mouse Slc39a10 and Slc30a genes in BMDMs obtained from wild-type mice treated with LPS (Fig. 1 C and D). Consistent with patients’ data, the expression of Slc39a10 was significantly down-regulated following LPS stimulation.

Generation of Macrophage-Specific Slc39a10-Knockout Mice. Next, to study the function of Slc39a10 in macrophages, we generated macrophage-specific Slc39a10-knockout (Slc39a10fl/fl;LysM-Cre+) mice using Cre recombinase driven by the myeloid cell-specific lysozyme M promoter (LysM-Cre) (Fig. S1). Loss of Slc39a10 expression was confirmed by a 95% reduction in Slc39a10 mRNA levels in PMs of Slc39a10fl/fl;LysM-Cre+ mice compared with control (Slc39a10fl/fl) mice (Fig. 2A). We then used inductively coupled plasma mass spectrometry (ICP-MS) to measure the intracellular concentration of various metals in BMDMs obtained from Slc39a10fl/fl;LysM-Cre+ and control mice. Importantly, of the 15 metals examined, only Zn was significantly lower in Slc39a10fl/fl;LysM-Cre+ BMDMs, and the difference between Slc39a10fl/fl;LysM-Cre+ and control BMDMs was even larger following Zn supplementation (Fig. 2B). These results support the notion that Slc39a10 transports primarily Zn in mouse macrophages, which is consistent with previous reports that suggested Slc39a10 functions as a Zn importer in various cell types (6–8, 18).

Reduced LPS-Induced Mortality in Slc39a10fl/fl;LysM-Cre+ Mice. Next, we examined the function of Slc39a10 in macrophages in response to LPS. Slc39a10fl/fl;LysM-Cre+ offspring were born at the expected Mendelian ratio and did not develop any overt phenotype during 12 mo of observation under normal conditions. However, when we stimulated Slc39a10fl/fl;LysM-Cre+ and control mice with a combination of LPS and β-galactosamine (19), the Slc39a10fl/fl;LysM-Cre+ mice had significantly higher survival rate (Fig. 2C); specifically, the 12-h survival rate of Slc39a10fl/fl;LysM-Cre+ mice and control mice was 80.0% and 27.3%, respectively. Upon LPS stimulation, activation of inflammatory molecules can lead to liver damage (20). As expected, 6 h after LPS stimulation, serum alanine transaminase (ALT) and aspartate aminotransferase (AST) levels were increased, and both ALT and AST levels were higher in control mice than in Slc39a10fl/fl;LysM-Cre+ mice (Fig. 2D). Serum ALT (D), serum AST (E), and liver H&E staining (F) in the indicated mice either with or without LPS stimulation (n = 5). Scale bars in F: 50 μm. n.d., not detectable. NT, no treatment. A and B were analyzed by t test, C by log-rank test, and D and E by ANOVA. *P < 0.05; **P < 0.01.

Serum, but Not Macrophage, Cytokine Levels Are Significantly Decreased in Slc39a10fl/fl;LysM-Cre+ Mice. Toll-like receptor 4 (TLR4) is the principal receptor for LPS, and activation of TLR4 can increase susceptibility to sepsis, as evidenced by the hyperactivated immune response (the so-called “cytokine storm”) that is often responsible for the death of the host. TLR4 signals via both MyD88-dependent and MyD88-independent pathways (21, 22). We therefore measured cytokine levels of both pathways in Slc39a10fl/fl;LysM-Cre+ and control mice. Six hours after LPS stimulation, the levels of major cytokines were significantly reduced in the sera and spleens of Slc39a10fl/fl;LysM-Cre+ mice compared with control mice (Fig. 3 A and B). These results indicate that the loss of Slc39a10 in macrophages regulates cytokine expression, which may explain the resistance of Slc39a10fl/fl;LysM-Cre+ mice to LPS-induced mortality.

We also measured cytokine expression in BMDMs obtained from LPS-stimulated mice. Surprisingly, we found that LPS stimulation induced similar levels of proinflammatory cytokines in the BMDMs of Slc39a10fl/fl;LysM-Cre+ and control mice (Fig. 3 C and D), suggesting that deleting Slc39a10 expression in macrophages does not affect their ability to produce these cytokines.

Slc39a10fl/fl;LysM-Cre+ Mice Have Reduced Numbers of Macrophages. Next, we measured the total number of monocytes in LPS-stimulated Slc39a10fl/fl;LysM-Cre+ and control mice. Interestingly, LPS stimulation reduced the number of monocytes in Slc39a10fl/fl;LysM-Cre+
mice compared with control mice but had no significant effect on the number of neutrophils (Fig. 4A), a cell type that also expresses the LysM promoter (23). In addition, the percentage of inflammatory macrophages (measured as F4/80+ cells) was significantly lower in thiglycollate-elicted PMs and BMDMs from LPS-stimulated Slc39a10fl/fl;LysM-Cre+ mice compared with respective controls (Fig. 4B and C). We further examined the affected macrophage subtypes (24, 25) using flow cytometry (Fig. 4D) and qPCR (Fig. S24). We found that M1 macrophages were significantly reduced in Slc39a10fl/fl;LysM-Cre+ mice, whereas the number of M2 macrophages was unchanged.

Consistent with this finding, immunohistochemistry revealed reduced infiltration of F4/80+ macrophages in the spleen and the liver of LPS-treated Slc39a10fl/fl;LysM-Cre+ mice (Fig. 4E). Moreover, the number of circulating F4/80+ macrophages was significantly lower in Slc39a10fl/fl;LysM-Cre+ mice than in control mice (Fig. 4F). In addition, the number of Ly6C+ monocytes, from which inflammatory macrophages are derived (26), was also lower in the bone marrow of Slc39a10fl/fl;LysM-Cre+ mice compared with control mice (Fig. 4F). Finally, the number of splenic F4/80+ macrophages was lower in the Slc39a10fl/fl;LysM-Cre+ mice than in control mice (Fig. 4F). Taken together, these results suggest that deleting Slc39a10 expression in macrophages leads to decreased numbers of monocytes and macrophages during the inflammatory response.

LPS Stimulation Induces Macrophage Apoptosis in Slc39a10fl/fl;LysM-Cre+ Mice. Next, we investigated the mechanism by which Slc39a10 regulates macrophages by measuring the proliferation and apoptosis of F4/80+ macrophages using BrdU incorporation and annexin V/propidium iodide (PI) staining, respectively. We found that the rate of macrophage proliferation was similar in LPS-stimulated Slc39a10fl/fl;LysM-Cre+ and LPS-stimulated control mice; however, Slc39a10fl/fl;LysM-Cre+ macrophages had a significantly higher level of apoptosis (Fig. 5A and B). Moreover, further analyses suggested that this increased apoptosis occurred primarily in M1 macrophages (Fig. S2B).

We also measured markers of other types of cell death, including pyroptosis [caspase-1 (27)], necroptosis [MLKL (28)], autophagy [LC3 (29)], and ferroptosis [Plg2 mRNA and lipid peroxidation (30)] in LPS-stimulated Slc39a10fl/fl;LysM-Cre+ and control macrophages. As shown in Fig. S3, the levels of these molecular markers were similar in Slc39a10fl/fl;LysM-Cre+ and control macrophages. We then examined the effects of specific inhibitors of various types of cell death on the viability of Slc39a10fl/fl;LysM-Cre+ macrophages. As shown in Fig. 5C, only Z-VAD-FMK, an inhibitor of apoptosis (31), significantly rescued LPS-induced macrophage death; in contrast, inhibitors of necroptosis (necrostatin), autophagy (3-methyladenine), and ferroptosis (Ferr-1) (31) had no such effect.

Slc39a10 Deficiency Does Not Affect Phagocytosis or the E. coli-Killing Capacity of Macrophages. Given that Zn has been reported to affect the phagocytosis of E. coli by PMs (3), we examined the phagocytic capacity of Slc39a10fl/fl;LysM-Cre+ and control macrophages. However, we found no significant difference with respect to phagocytosis or E. coli-killing capacity in Slc39a10fl/fl;LysM-Cre+ and control cells (Fig. S4A). Because rapid bacterial clearance plays an important role in the host’s survival during infection, we also analyzed the survival rates of Slc39a10fl/fl;LysM-Cre+ and control mice following E. coli infection. Interestingly, the mortality rate was considerably higher in the Slc39a10fl/fl;LysM-Cre+ mice (Fig. 5D). Further analysis revealed the presence of more E. coli cfus in various tissues of Slc39a10fl/fl;LysM-Cre+ mice at 12 h after infection (Fig. S4B). Collectively, these data suggest that the increased bacterial burden and mortality in E. coli-infected Slc39a10fl/fl;LysM-Cre+ mice could be attributed to the function of Slc39a10 in controlling the number of macrophages.

p53 Protein Stability Is Increased in the Macrophages of LPS-Stimulated Slc39a10fl/fl;LysM-Cre+ Mice. Because p53 is the master transcription factor that controls apoptosis, we measured the expression of p53 in LPS-stimulated Slc39a10fl/fl;LysM-Cre+ and LPS-stimulated control mice. Our analysis revealed that p53 protein levels were ~2.6-fold higher in Slc39a10fl/fl;LysM-Cre+ macrophages than in control macrophages.
mice with the p53-specific inhibitor pifithrin-α and no. 49 by ANOVA, vol. 114 < by log-rank test. * macrophages than control mice (Fig. 5). Finally, we examined the role of Zn on endotoxin resistance in mice following LPS stimulation. The mRNA levels of Mt1, a cellular Zn biomarker, were also lower in Slc39a10<sup>fl/fl</sup>;LysM-Cre<sup>–/–</sup> PMs and BMDMs than in Slc39a10<sup>fl/fl</sup>;LysM-Cre<sup>–/–</sup> macrophages compared with Slc39a10<sup>fl/fl</sup>;LysM-Cre<sup>–/–</sup> macrophages. Next, we examined the role of Zn on endotoxin resistance in mice following LPS stimulation compared with vehicle-treated mice (Fig. 7D and E). In contrast, treating wild-type mice with the membrane-permeable Zn-specific chelator TPEN [N,N′-tetraakis (2-pyridylmethyl) ethylenediamine] significantly reduced LPS-induced mortality and liver damage, and these protective effects of TPEN were largely prevented by Zn supplementation (Fig. 7F and G). Moreover, TPEN treatment decreased the percentages of Ly6C<sup>+</sup> monocytes and F4/80<sup>+</sup> macrophages, and both of these effects were reversed by Zn supplementation (Fig. 7H). Furthermore, TPEN increased apoptosis in wild-type BMDMs, and this effect was reversed by Zn supplementation. In contrast, TPEN had little effect on apoptosis in p53<sup>−/−</sup>;LysM-Cre<sup>–/–</sup> macrophages (Fig. 7I). In addition, TPEN stabilized the p53 protein in both Slc39a10<sup>fl/fl</sup> mice.
macrophages (Fig. 5H) and wild-type macrophages (Fig. S6). Together, these results indicate that Scl39a10 modulates LPS-induced apoptosis and endotoxin resistance in macrophages through regulating intracellular Zn homeostasis.

Discussion

Here, we report that the metal transporter SLC39A10 plays an important role in mediating macrophage survival by controlling the cellular import of Zn in a p53-dependent manner. Fukuda and coworkers (7, 8) recently reported that Scl39a10 plays a role in B cells. In pro-B cells, loss of Scl30a10 led to increased caspase activity that was accompanied by reduced intracellular Zn, resulting in reduced cell death (7). In mature B cells, the authors found that Scl39a10 selectively regulates B cell apoptosis; this increased inhibiting apoptosis in these cells (41); however, precisely how these dynamic processes underlie the survival and death of macrophages remains unknown. We found that treating mice with a Zn-chelating agent led to increased cell death among monocytes and macrophages as well as up-regulated p53 signaling, in response to LPS stimulation. In our working model (Fig. S7), we propose that SLC39A10-mediated Zn influx in macrophages is essential for maintaining cell survival during the inflammatory response. In the absence of SLC39A10, Zn deficiency leads to the cytoplasmic accumulation of p53 and the nuclear translocation of AIF, which in turn triggers apoptosis.

On the other hand, Zn supplementation can improve the outcome of many infectious diseases, as shown using both animal models and clinical data (2). However, our $\text{Slc39a10}^{-/-}\text{LysM-Cre}^+$ mice have improved survival following LPS stimulation. Moreover, Zn chelation treatment increased survival following LPS stimulation, and this beneficial effect was prevented by Zn supplementation. These seemingly contradictory findings may be attributed to distinct effects of Zn on processes activated by different inflammatory stimuli. Notably, we found that $\text{Slc39a10}^{-/-}\text{LysM-Cre}^+$ mice were more sensitive to E. coli infection than $\text{Slc39a10}^{+/+}$ mice; this increased
susceptibility is likely due to reduced macrophage numbers and the resulting reduction in total phagocytic capacity. Following bacterial infection, the host’s survival requires the rapid clearance of the pathogen by phagocytic cells. Nevertheless, activated macrophages also produce and release large quantities of inflammatory cytokines. Once the immune response is overactivated, it can be detrimental to the host. Our LPS stimulation model recapitulates this immune response, where multiple macrophages led to reduced numbers of stimulated macrophages following LPS exposure, which decreased serum cytokines and helped to protect the liver from subsequent damage.

Given that our macrophage-specific Slc39a10-deficient mice have considerable numbers of macrophages that respond to LPS, other Zn transporters are likely to have a compensatory function, thereby fine-tuning the immune response of macrophages during inflammatory stimuli. Future studies should explore the potential role(s) of other Zn transporters in regulating macrophage function and mediating host defense during an inflammatory event.

Materials and Methods

All animal experiments were approved by the Institutional Animal Care and Use Committee of Zhejiang University. The generation of Slc39a10fl/fl,LysM-Cre, p53fl/fl,LysM-Cre, and DKO (p53fl/fl,Slc39a10fl/fl,LysM-Cre) mice, iCP-MS analysis, and methods used in the collection and culture of primary macrophages, PMs, and BMDMs, fluo-3 AM staining, immune cell classification, cell-viability assay, phagocytosis, and E. coli-killing experiments are presented in SI Materials and Methods. Except where indicated otherwise, summary data are expressed as the mean ± SEM. The log-rank test was used to analyze the survival curves, and the Student’s t test was used to compare two groups. Multiple group comparisons were conducted by one-way ANOVA with Tukey’s post hoc test. A P value <0.05 was considered statistically significant.

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