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CUTTING EDGE

Cutting Edge: The SLAM Family Receptor Ly108 Controls T Cell and Neutrophil Functions[1]

Duncan Howie,[2] F. Stephen Laroux,* Massimo Morra,* Abhay R. Satoskar,† Lucia E. Rosas,† William A. Faubion,[3]* Aimee Julien,* Svend Rietdijk,* Anthony J. Coyle,‡ Christopher Fraser,§ and Cox Terhorst**

Ly108, a glycoprotein of the signaling lymphocytic activation molecule family of cell surface receptors expressed by T, B, NK, and APCs has been shown to have a role in NK cell cytotoxicity and T cell cytokine responses. In this study, we describe that CD4$^+$ T cells from mice with a targeted disruption of exons 2 and 3 of Ly108 (Ly108$^{\Delta E2+3}$) produce significantly less IL-4 than wild-type CD4$^+$ cells, as judged by in vitro assays and by in vivo responses to cutaneous infection with* Leishmania mexicana*. Surprisingly, neutrophil functions are controlled by Ly108. Ly108$^{\Delta E2+3}$ mice are highly susceptible to infection with* Salmonella typhimurium*, bactericidal activity of Ly108$^{\Delta E2+3}$ neutrophils is defective, and their production of IL-6, IL-12, and TNF-α is increased. The aberrant bactericidal activity by Ly108$^{\Delta E2+3}$ neutrophils is a consequence of severely reduced production of reactive oxygen species following phagocytosis of bacteria. Thus, Ly108 serves as a regulator of both innate and adaptive immune responses. The Journal of Immunology,* 2005, 174: 5931–5935.

The signaling lymphocytic activation molecule (SLAM)[4] family of immune receptors, which includes the SLAM-associated protein (SAP)-binding receptors SLAM, Ly108, CD84, CS1, Ly-9, 2B4, CD48, BLAME, and SF2001, are thought to play a role in innate and adaptive immunity (1, 2). Ly108 (NTB-A, SF2000, KALI, SF-3) is a membrane glycoprotein of the SLAM family expressed on T cells, B cells, macrophages, dendritic cells, and granulocytes (3–5). Ly108 has been shown to function on NK cells by augmenting cytotoxicity (4); this function is impaired in NK cells derived from X-linked lymphoproliferative disease patients who lack expression of the adapter SAP. A recent report suggests that anti-Ly108 Ab cross-linking induces IFN-γ production by T cells (6). Both Ly108 and SLAM are homotypic adhesion receptors with two cytoplasmic immunoreceptor tyrosine-based switch motif domains which are tyrosine-phosphorylated upon receptor cross-linking (6, 7). The cell and tissue distribution of SLAM and Ly108 are very similar and T cell IFN-γ responses are augmented by Abs against either receptor (8, 9). T cell signals mediated by SLAM are partially regulated by the adapter SAP (SH2D1A), which binds to the immunoreceptor tyrosine-based switch motif domains in the receptors' cytoplasmic tail, inducing activation of Fyn and downstream phosphorylation of Dok1/2, SH2-containing protein, Ras-GTPase-activating protein, and SHIP in T cells (7, 10, 11). EWS/FL11-associated transcript 2 is structurally related to SAP and thought to have a similar function in APCs (1, 12).

We have recently demonstrated that mice deficient in SLAM have impaired macrophage responses to LPS stimulation and diminished Th2 cytokine production (2). Because an IL-4 defect is also observed in CD4$^+$ cells from mice deficient in SAP and because this defect appears to be more robust in SAP-deficient animals than in SLAM-deficient mice, we hypothesize that other SLAM-related receptors might have a similar phenotype (13, 14). This prompted us to investigate the role of Ly108 in adaptive and innate immune responses. In this study, we report that in a mouse with a targeted disruption of the Ly108 gene CD4$^+$ T cell and innate responses are defective. The results of these studies demonstrate a surprising role for Ly108 in the control of responses to bacteria by neutrophils while macrophage functions are intact.

Materials and Methods

Generation of Ly108-deficient (Ly108$^{\Delta E2+3}$) mice

A targeting construct was generated from a 129/Sv mouse pBAC clone (CD84.361) and was cloned into the plasmid vector pPNT. The second and third exons of the Ly108 gene, encoding the complete ectodomain of Ly108, were replaced with the neomycin resistance gene.

The targeting vector was linearized and electroporated into embryonic stem (ES) cells. G418-resistant ES cell colonies were screened by Southern blot. *Spe*I digestion of genomic DNA generated a 12-kb band from the

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[4] Abbreviations used in this paper: SLAM. signaling lymphocytic activation molecule; SAP, SLAM-associated protein; ROS, reactive oxygen species; TEPM, thioglycolate-elicited peritoneal macrophage; ES, embryonic stem; WT, wild type; PMN, polymorphonuclear neutrophil; PGN, peptidoglycan.

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endogenous wild-type (WT) Ly108 allele, while the correctly targeted Ly108 allele generated an additional 6.1-kb band (Fig. 1, *A* and *B*). The single integration site was confirmed with the internal 5′ probe upon *Spe*I digestion of the DNA (our unpublished data). A $Ly108^{+/-}$ ES cell clone was injected into C57BL/6 blastocysts. F_1 mice with germline transmission of $Ly108^{+/-}$ (C57BL/6 × 129/Sv) were bred to homozygosity. $Ly108^{\Delta E2+3}$ mice were kept under specific pathogen-free conditions.

Mice were genotyped by genomic PCR. Primers P1–P4 were used for typing, P1 and P2 amplify the second exon, giving a 540-bp band, while P3 and P4 amplify the neomycin gene to produce a 700-bp band (Fig. 1*B*). The sequences are: P1, 5′-GAGACCATAAGTTAGGATCATC-3′; P2, 5′-CAGTGTATGATCCTGTGTCTG-3′; P3, 5′-GCAGCGCATCGCCTTC TATC-3′; and P4, 5′-CACCTAGATCTCTTACTCCTC-3′. All mice in this study were of the C57BL/6 × 129sv background; control mice (C57BL/6 × 129sv F_1) were purchased from The Jackson Laboratory.

RT-PCR

RT-PCR was performed as previously described (2, 8) Ly108 fragments spanning exons 2 and 3 were amplified using a 5′ primer in exon 2 which was 5′-GGGAAGATAGCCAATATCATCAT-3′ and 3′ primer in exon 3 which was 5′-GCAGAGACTCTGGGTCGAAA-3′. Fragments spanning exons 1–8 were amplified with a 5′ primer TCAGAGGATGGTCTGG CTCT in exon 1 and a 3′ primer AGCGTGTGGATGAGTTACCC in exon 8.

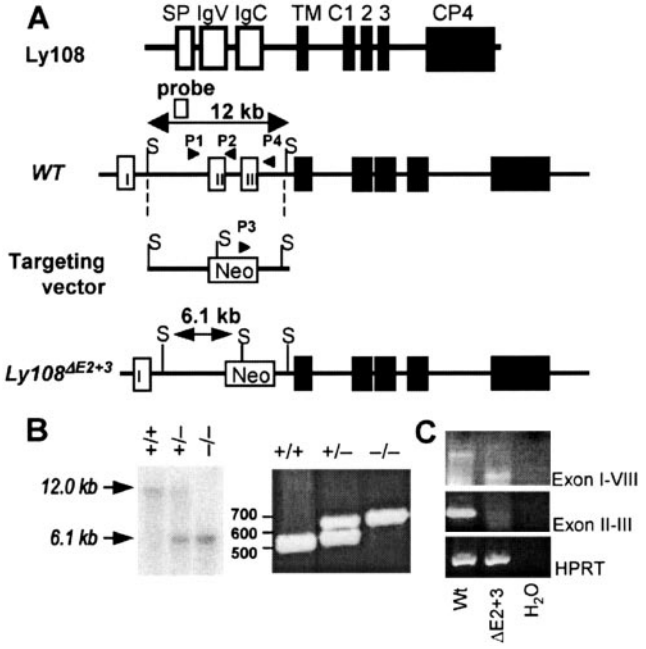

FIGURE 1. Targeted disruption of the mouse Ly108 gene. *A,* The targeting vector. The mouse Ly108 genomic locus, Ly108 targeting vector, and chromosomal locus after homologous recombination with the targeting vector. The second and third exons of the Ly108 gene encoding the entire ectodomain of Ly108 were replaced with a neomycin resistance cassette. The locations of the Southern blot probe and four oligonucleotide primers, P1–P4, used for genomic PCR typing and the *Spe*I sites used for Southern blot digestion are shown. SP, Signal peptide; IgV, IgV set domain; IgC, IgC set domain; TM, transmembrane domain; CP1,2,3,4, cytoplasmic domains. *B,* Genomic Southern blot and PCR analysis. *Left panel,* Screening for homologous recombination by Southern blot digestion with *Spe*I. The WT Ly108 locus produces a 12-kb fragment using the probe shown. The targeted locus produces a 6.1-kb fragment. *Right panel,* Screening for homologous recombination events by genomic PCR using primers P1–P4. Each sample was amplified with a mixture of primers P1–P4. A 540-bp band is detected in WT and heterozygote mice. A 700-bp band, which results from amplification of the Neo gene is detected in knockouts and heterozygotes. *C,* RT-PCR analysis. RT-PCR products were generated from the thymus of WT and $Ly108^{\Delta E2+3}$ mice. A 450-bp band encoding the second and third exons is detectable in WT mice but absent in $Ly108^{\Delta E2+3}$ mice. A full-length 1.2-kb band is detectable using primers spanning exons 1–8 in WT and a 650-bp band is present in the $Ly108^{\Delta E2+3}$ mice.

T cell stimulation proliferation assays and Th1/Th2 polarization

T cell stimulation, proliferation assays, and Th1/Th2 polarization were performed as previously described (2, 8).

ELISA for T cell, polymorphonuclear neutrophils (PMNs), and macrophage cytokine secretion

ELISA quantitation of cytokines in tissue culture supernatants or serum was performed as previously described (2, 8).

Infection with Leishmania mexicana

L. mexicana infections were performed as previously described (15). Lesion diameter was measured at 1-wk intervals for up to 8 wk.

Infection with Salmonella typhimurium

WT and $Ly108^{\Delta E2+3}$ mice were challenged i.p with 1×10^5 CFU of *S. typhimurium* 14028s or *sseB,* an attenuated isogenic mutant of the 14028s strain of *S. typhimurium*. Mice were injected i.p. with 1×10^5 bacteria in 2 ml of PBS. Blood samples were taken from the tail vein at 24 h for cytokine analysis. Time to death was recorded.

Isolation of macrophages and PMNs

Thioglycolate-elicited macrophages (TEPM) were obtained as previously described (2). PMNs were isolated from bone marrow or alternatively from the peritoneum 4 h after injection with 2 ml of 5% Brewer's thioglycolate medium. Bone marrow or thioglycolate peritoneal lavage was washed three times in HBSS/5% FCS. PMNs were then isolated by discontinuous Percoll gradient centrifugation. Using this technique, >95% purity was routinely obtained as assessed by Wright-Giemsa staining.

Gentamicin-protection bacterial killing assay

Macrophage bactericidal activity was measured using a gentamicin protection assay as previously described (2).

PMN opsono-phagocytic killing assay

Bone marrow-derived or peritoneal-derived PMNs were washed three times in HBSS/5% FCS before re-suspension at 1×10^6 in HBSS supplemented with 50% fresh autologous mouse serum. Bacteria opsonized in 20% fresh normal mouse serum at 37°C for 30 min were added to the PMNs at ratios of 3:1, 2:1, or 1:1 PMNs:bacteria and incubated at 37°C with end-over-end mixing. Fifty-microliter aliquots were extracted at 0, 30, 60, 90, and 120 min and lysed in 10 ml of sterile water for 15 min at 25°C. Twenty microliters was then plated directly onto Luria-Bertani agar plates, and bacterial colonies were counted after an 18-h incubation at 37°C.

Flow cytometric measurement of PMN phagocytosis

Bone marrow-derived PMNs (4×10^6/ml in HBSS/5% FCS) were incubated for various periods with 4×10^8 paraformaldehyde-fixed and opsonized GFP-expressing *Escherichia coli* strain MS589 (a kind gift from Dr. P. Klemm, Technical University of Denmark, Lyngby, Denmark). Cells were washed three times in ice-cold PBS followed by a 60-s wash in 0.4% trypan blue to quench extracellular GFP and a final wash in PBS before flow cytometry. As a negative control for nonspecific bacterial-PMN adhesion, a portion of the PMNs was fixed for 10 min in 2% paraformaldehyde before the assay.

Measurement of superoxide generation

Superoxide production was measured with lucigenin. PMNs and macrophages resuspended in HBSS/5% FCS at 2.5×10^5 and 1×10^6/ml, respectively, were stimulated for 3 h with 8×10^7 heat-killed, opsonized *E. coli* strain F18 or PMA at 1 μg/ml for 15 min. Luminescence was measured with a TD2020 luminometer (Turner Designs).

Results and Discussion

Generation of $Ly108^{\Delta E2+3}$ mice

A mouse with a targeted disruption of the second and third exons of Ly108, encoding its entire ectodomain, was generated by homologous recombination in ES cells (Fig. 1, *A* and *B*). $Ly108^{\Delta E2+3}$ mice were fertile, morphologically indistinguishable from WT littermates, and no differences in T, B, or NK development were detected by cell surface marker analysis (our

unpublished data). No transcripts encoding Ly108 exons 2 and 3 mRNA was detected by RT-PCR in knockout thymus (Fig. 1*C*). A 650-bp transcript was detectable with primers spanning the signal peptide to the 3′ untranslated region, indicating that a short residual transcript encoding the transmembrane and cytoplasmic domain remained in these mice. Since Ly108 is a self-ligand, it was anticipated that removal of the entire extracellular portion of the receptor would result in a total loss of Ly108 function. It is possible however that the Ly108$^{\Delta E2+3}$ mutation results in a different phenotype from a Ly108^{null} mouse.

Impaired IL-4 production by Ly108$^{\Delta E2+3}$ CD4$^+$ T cells

To determine whether Ly108$^{\Delta E2+3}$ T cells deviated in their cytokine production in a way similar to those derived from SLAM$^{-/-}$ and SAP$^{-/-}$ mice, we performed various in vitro and in vivo analyses. First, splenic CD4$^+$ T cells were stimulated in vitro with anti-CD3 and anti-CD28 or PMA and ionomycin, followed by analysis of cell supernatant cytokines using ELISA. Ly108$^{\Delta E2+3}$ CD4$^+$ T cells produce significantly less IL-4 than WT T cells even after PMA/ionomycin stimulation, whereas production of IFN-γ was normal (Fig. 2*A*). Ly108$^{\Delta E2+3}$ CD4$^+$ T cells stimulated with anti-CD3 Abs also produced less IL-13 than WT T cells as assessed by semiquantitative cytokine array analysis (our unpublished data). Ly108$^{\Delta E2+3}$ CD8$^+$ T cell production of IFN-γ did not differ from WT CD8$^+$ T cells (our unpublished data). We next determined whether the observed defect in IL-4 production by Ly108$^{\Delta E2+3}$ CD4$^+$ T cells could be "rescued" by a secondary stimulation or by Th2 polarization. Following secondary stimulation, IL-4 production by Ly108$^{\Delta E2+3}$ CD4$^+$ T cells was still lower and IL-4 production following Th2 polarization was ~50% of that of WT CD4$^+$ T cells (Fig. 2*B*). Conversely, polarization of CD4$^+$ T cells toward a Th1 phenotype resulted in equivalent IFN-γ production by CD4$^+$ T cells from WT and Ly108$^{\Delta E2+3}$ mice (Fig. 2*B*). The proliferative response of Ly108$^{\Delta E2+3}$ CD4$^+$ T cells to anti-CD3/CD28 stimulation was normal (our unpublished observations).

To confirm the defect in IL-4 production in vivo, we analyzed the ability of Ly108$^{\Delta E2+3}$ mice to mount an inflammatory response to infection with *L. mexicana*. Th2 responses upon infection with *L. mexicana* are a prerequisite for controlling the progression of lesions caused by the parasite and consequently serves as a useful indicator for the correct balance of Th1 and Th2 responses (16). Whereas IL-4 is necessary for lesion formation, IFN-γ production is required for protective host immunity after *L. mexicana* infection (17–19). In IL-4$^{-/-}$ mice, Th1 responses are predominant, which results in healing of the lesions (17). Ly108$^{\Delta E2+3}$ mice infected with *L. mexicana* exhibited delayed formation of lesions compared with WT mice (5 wk in Ly108$^{-/-}$ animals, 3 wk in WT) and developed significantly smaller lesions (Fig. 2*D*). In vitro Ag restimulation of lymph node CD4$^+$ T cells from the *L. mexicana*-infected mice revealed lower IL-4 production by the Ly108$^{\Delta E2+3}$ T cells (536 ± 124 vs 229 ± 35 pg/ml). This result was consistent with the in vitro observation of impaired IL-4 production by CD4$^+$ T cells. Thus, in Ly108$^{\Delta E2+3}$, SLAM$^{-/-}$, and SAP$^{-/-}$ mice Th2 functions are impaired; the Ly108$^{\Delta E2+3}$ phenotype is more robust than observed in the SLAM$^{-/-}$ mouse, since IL-4 production is impaired even upon stimulation with PMA and ionomycin (13).

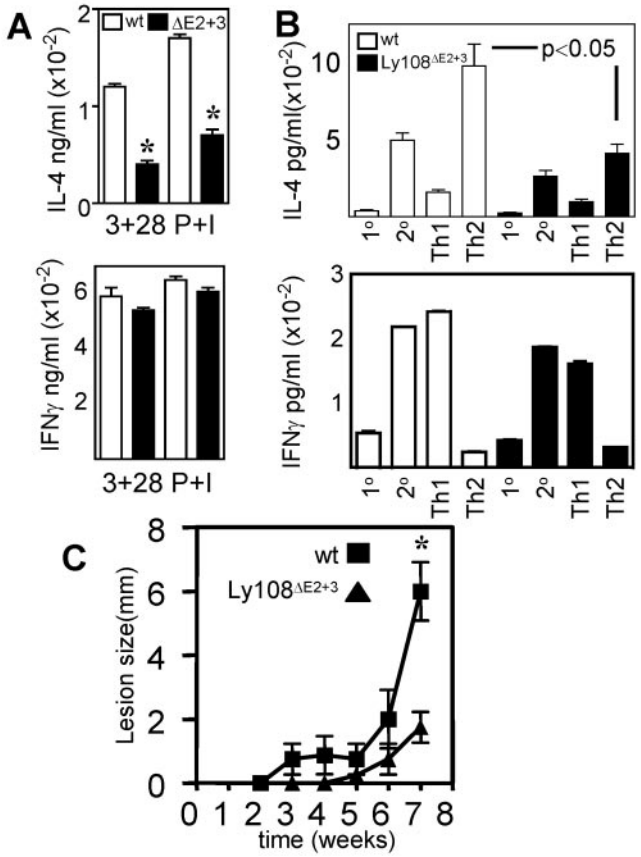

FIGURE 2. Impaired production of IL-4 and reduced inflammatory response to *L. mexicana* infection in the absence of Ly108. *A,* Reduced IL-4 production by CD4$^+$ T cells in the absence of Ly108. CD4$^+$ T cells from WT and Ly108$^{\Delta E2+3}$ mice were stimulated as described in *Materials and Methods*. IL-4 and IFN-γ in the culture supernatants were measured by ELISA. Results are representative of three separate experiments. P+I, PMA + ionomycin. *B,* Reduced IL-4 production by Ly108$^{\Delta E2+3}$ CD4$^+$ cells after Th2 polarization. CD4$^+$ T cells from WT and Ly108$^{\Delta E2+3}$ mice were stimulated under Th1 and Th2 conditions outlined in *Materials and Methods.* IL-4 and IFN-γ in cell culture supernatants were measured by ELISA. *C,* Reduced inflammatory response to cutaneous *L. mexicana* infection in Ly108$^{\Delta E2+3}$ mice. WT and Ly108$^{\Delta E2+3}$ mice were infected with 5×10^6 amastigotes of *L. mexicana* by s.c. injection into the rump. Lesion size was measured by mean lesion diameter in WT (■) and Ly10$^{\Delta E2+3}$ (▲) mice following *L. mexicana* infection for 7 wk. Data are represented as mean ± SE. *, $p < 0.05$.

Increased susceptibility to bacterial infection in the absence of Ly108

Because we had observed altered innate immune responses and, in particular, a macrophage defect in SLAM$^{-/-}$ mice (2), we next examined a role for Ly108 in innate immunity. To this end, WT and Ly108$^{\Delta E2+3}$ mice were infected i.p with 1×10^5 of *S. typhimurium* 14028s or a congenic *sseB* mutant of *S. typhimurium*, deficient in the SPI2-encoded type III secretory system. *S. typhimurium sseB* is attenuated for virulence and is therefore cleared efficiently by WT mice. Twenty-four hours after infection with 14028s, Ly108$^{\Delta E2+3}$ mice displayed signs of severe salmonellosis including hunching, pilial erection, and lethargy. WT controls appeared to be healthy. Ly108$^{\Delta E2+3}$ mice suffered from accelerated morbidity in response to the WT *S. typhimurium* strain 14028s (100% succumbed to infection in 3 days vs 5 days for WT mice; Fig. 3*A*) and displayed unusual sensitivity to the attenuated *sse*B strain (40% of Ly108$^{\Delta E2+3}$ mice succumbed to infection vs no WT animals). Analysis of

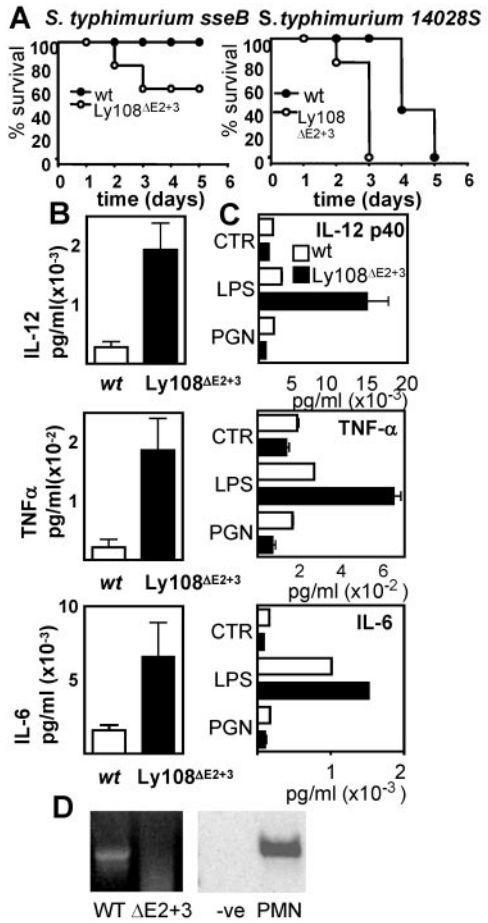

FIGURE 3. Increased susceptibility of Ly108$^{\Delta E2+3}$ mice to infection with *S. typhimurium*. *A,* Survival of Ly108$^{\Delta E2+3}$ mice after infection with *S. typhimurium* 14028s or *sse*B. WT and Ly108$^{\Delta E2+3}$ mice (n = 5/group) were infected with *S. typhimurium* as described in *Materials and Methods*. Time to death was recorded. *B,* Serum proinflammatory cytokines in *S. typhimurium*-infected Ly108$^{\Delta E2+3}$ mice. Sera from the mice infected with *S. typhimurium sse*B were collected at 24 h postinfection. Cytokines were measured by ELISA. Data represent the mean ± SE from five mice. *C,* PMN cytokine production in response to LPS and PGN stimulation. Bone marrow PMNs from WT and Ly108$^{\Delta E2+3}$ mice were stimulated for 24 h with LPS (100 ng/ml) or PGN (1 μg/ml). Cytokines were measured by ELISA. *D,* Ly108 expression by peritoneal macrophages and bone marrow neutrophils. RT-PCR of Ly108 on RNA derived from TEPM (*left panel*) and bone marrow PMNs (*right panel*). CTR, Control.

serum cytokines in *S. typhimurium seeB*-infected Ly108$^{\Delta E2+3}$ mice showed a 4- to 7-fold increase over WT mice in the amounts of circulating IL-12p40, TNF-α, and IL-6 (Fig. 3*B*).

We next investigated the possibility that increased susceptibility to bacterial infection in Ly108$^{\Delta E2+3}$ mice might be due to aberrant neutrophil or macrophage responses. Bone marrow PMNs were tested for in vitro cytokine production in response to stimulation with bacterial (*E. coli*) LPS and peptidoglycan (PGN) from *Staphylococcus aureus* (Fig. 3*C*). Surprisingly, PMNs from Ly108$^{\Delta E2+3}$ mice produced 5-fold more IL-12p40 than WT PMNs in response to LPS and twice as much TNF-α. IL-6 production was also moderately elevated by PMNs from Ly108$^{\Delta E2+3}$ mice. Cytokine production by macrophages was, however, not significantly different between WT and Ly108$^{\Delta E2+3}$ mice (our unpublished observations). Cytokine production by neutrophils in response to PGN did not increase significantly above constitutive levels, and no differences were observed between WT and Ly108$^{\Delta E2+3}$ neutrophils in this respect, despite PGN inducing robust TNF-α responses in both WT and Ly108$^{\Delta E2+3}$ macrophages (our unpublished data). Both bone marrow neutrophils and peritoneal macrophages expressed Ly108 mRNA (Fig. 3*D*).

We then tested the Ly108$^{\Delta E2+3}$ PMNs ability to phagocytose and kill bacteria. As shown in Fig. 4*A*, PMNs from Ly108$^{\Delta E2+3}$ mice were impaired in their bactericidal activity, displaying a significant lag in time to clear bacteria in vitro. Killing of *S. aureus* was also diminished in PMNs from Ly108$^{\Delta E2+3}$ mice, as was killing of *E. coli* by thioglycolate-elicited peritoneal PMNs from Ly108$^{\Delta E2+3}$ mice (our unpublished data). To assess whether the defect in PMN killing in the absence of Ly108 was attributable to impaired uptake of bacteria, a flow cytometric analysis of phagocytosis was used. Ly108$^{\Delta E2+3}$ PMNs were

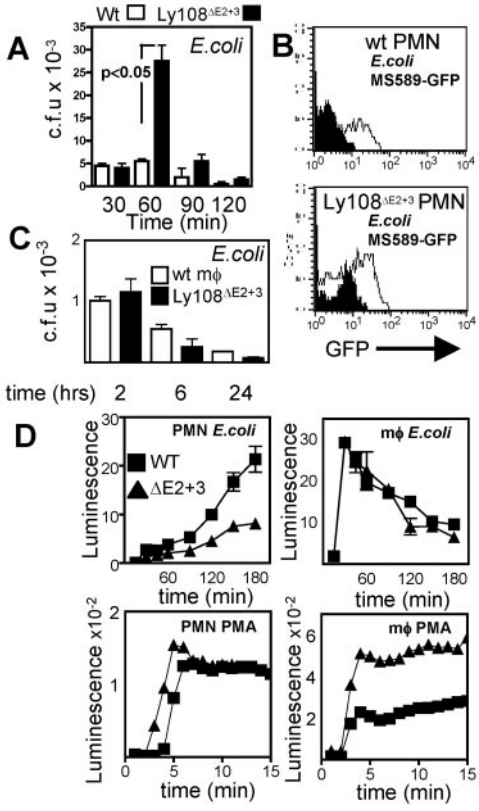

FIGURE 4. Killing of bacteria by PMNs, but not macrophages is impaired in the absence of Ly108. *A,* PMN bacterial killing. Measurement of in vitro killing of *E. coli* by bone marrow-derived PMNs from WT and Ly108$^{\Delta E2+3}$ mice by gentamicin protection assay. Results are expressed as internalized *E. coli* CFU/ml recovered from PMNs at the indicated times (starting inoculum 1 × 10^6 bacteria). Data are representative of five experiments. *B,* PMN phagocytosis. Phagocytosis of GFP-*E. coli* MS589 strain by WT and Ly108$^{\Delta E2+3}$ bone marrow PMNs. Filled histograms represent control PMNs fixed with paraformaldehyde before addition of bacteria. Unfilled histograms represent GFP fluorescence of bacteria internalized by PMNs. Data are representative of three experiments. *C,* Macrophage bacterial phagocytosis and killing. Killing of *E. coli* by TEPM from WT and Ly108$^{\Delta E2+3}$ mice using a gentamicin-protection assay. Data represent the mean ± SE of bacteria recovered from 1 × 10^6 macrophages (mϕ; starting inoculum 1 × 10^7 *E. coli*). Data are representative of three experiments. *D,* Production of ROS by Ly108$^{\Delta E2+3}$ PMNs and macrophages. Bone marrow-derived PMNs and TEPM from WT and Ly108$^{\Delta E2+3}$ mice were stimulated with heat-killed *E. coli* for 3 h or PMA for 15 min. Lucigenin luminescence was measured at the indicated periods. Data are representative of five experiments.

efficient in phagocytosis of paraformaldehyde-fixed GFP expressing *E. coli* (Fig. 4*B*). In contrast to PMNs, Ly108$^{\Delta E2+3}$ peritoneal macrophages were competent in both phagocytosis (2-h time point) and killing of bacteria after 6 and 24 h (Fig. 4*C*). Thus, Ly108$^{\Delta E2+3}$ PMNs are defective in their responses to bacteria, while macrophage functions appear normal.

Reduced PMN oxidative burst in the absence of Ly108

Following phagocytosis of bacteria, both PMNs and macrophages elicit a respiratory burst of reactive oxygen species (ROS) and NO into the bacteria-containing phagolysosome. To explain the significantly delayed bacterial killing by Ly108$^{\Delta E2+3}$ PMNs, we examined both their NO and ROS production. No difference in NO production in response to LPS and IFN-γ was observed between WT and Ly108$^{\Delta E2+3}$ PMNs (our unpublished data). However, a dramatic reduction in ROS production by Ly108$^{\Delta E2+3}$ PMNs in response to heat-killed *E. coli* was observed (Fig. 4*D*). As predicted by the bacterial killing experiments, production of ROS by Ly108$^{\Delta E2+3}$ macrophages in response to bacterial phagocytosis was normal. Analysis of ROS generation in response to PMA, a stimulus which bypasses receptor involvement, indicated that both PMNs and macrophages from Ly108$^{\Delta E2+3}$ mice made robust ROS responses equal to or, in the case of Ly108$^{\Delta E2+3}$ macrophages, exceeding that of WT cells.

In conclusion, we report here for the first time a critical role for the SLAM family receptor Ly108 in CD4$^+$ T cell responses and innate immunity to bacteria and parasites. This is the first report of the involvement of such a cell surface receptor in bacterial phagosomal killing. It will be of great interest to elucidate the biochemical mechanisms involved in Ly108 induction of cytokines in T cells and oxidative burst in PMNs.

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Disclosures

The authors have no financial conflict of interest.

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