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IL-25, IL-33 and TSLP receptor are not critical for development of experimental murine malaria

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ABSTRACT

IL-25, IL-33 and TSLP, which are produced predominantly by epithelial cells, can induce production of Th2-type cytokines such as IL-4, IL-5 and/or IL-13 by various types of cells, suggesting their involvement in induction of Th2-type cytokine-associated immune responses. It is known that Th2-type cytokines contribute to host defense against malaria parasite infection in mice. However, the roles of IL-25, IL-33 and TSLP in malaria parasite infection remain unclear. Thus, to elucidate this, we infected wild-type, IL-25^{-/-}, IL-33^{-/-} and TSLP receptor (TSLPR)^{-/-} mice with *Plasmodium berghei* (*P. berghei*) ANKA, a murine malaria strain. The expression levels of IL-25, IL-33 and TSLP mRNA were changed in the brain, liver, lung and spleen of wild-type mice after infection, suggesting that these cytokines are involved in host defense against *P. berghei* ANKA. However, the incidence of parasitemia and survival in the mutant mice were comparable to in the wild-type mice. These findings indicate that IL-25, IL-33 and TSLP are not critical for host defense against *P. berghei* ANKA.

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1. Introduction

Malaria, a parasitic disease caused by protozoa of the genus *Plasmodium*, is one of the world's three major infectious diseases, together with AIDS and tuberculosis. According to the WHO, approximately 200 million people are infected with malaria each year worldwide, and about 600 thousand people die annually [12,16]. In order to develop a prophylactic vaccine and therapeutic agents that have stable effects, it is necessary to analyze in detail and understand the inflammatory reaction that occurs during parasite infection.

Abbreviations: IL-25, interleukin-25; IL-33, interleukin-33; TSLPR, thymic stromal lymphoprotein receptor

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Following a bite and transmission into the blood by a malaria parasite-carrying mosquito of the genus anopheles, the parasites transmit the mammalian body in a form called sporozoites, then move into the hepatocytes through the bloodstream. This takes only a few minutes, making it difficult for the host's immune system to clear the parasites at this stage. In the hepatocytes, the sporozoites develop to the stage called merozoites. This development is obstructed by IFN- γ , produced by CD4⁺ T cells following antigen presentation by liver Kupffer cells or produced by CD8⁺ T cells following antigen presentation by the invaded hepatocytes, but this response is not very strong [21]. Merozoites enter the blood after destroying the hepatocytes, invade red blood cells, and then replicate and burst out. Host dendritic cells are activated by merozoite-derived antigens through pattern recognition receptors, and humoral- and cellular-immune responses are induced by various types of immune cells, including T cells, B cells, natural killer (NK) cells, NKT cells and macrophages. These immune

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responses are induced with the objective of parasite eradication, but they can also exacerbate the pathological condition. For example, proinflammatory cytokines such as IL-1, IL-6 and TNF released from activated dendritic cells and macrophages cause fever and severe malaria disease [21]. In addition, it has been reported that TNF released by monocytes, dependent on *Plasmodium falciparum*-specific IgE induced by a Th2 response, is involved in cerebral malaria and severe malaria disease [19]. Conversely, there is a report that IgE, increased by co-infection with helminths and not specific for malaria antigens, works to prevent cerebral malaria and severe malaria disease [13].

Experimental cerebral malaria (ECM) in mice infected with murine malaria parasites, *Plasmodium berghei* (*P. berghei*) ANKA, is broadly used as a model for human malaria caused by infection with *Plasmodium falciparum* [4]. So far, using this infection model, the relationship of malaria and immune responses has been studied using mice deficient in various genes, such as TLRs and Th1, Th2 and Th17 cytokines.

Mice deficient in TLR-1, TLR-2, TLR-3, TLR-4, TLR-6, TLR-7 or TLR-9, as well as MyD88, TIRAP and TRIF, which are adapter proteins of TLRs, showed similar susceptibility to wild-type mice to *P. berghei* ANKA infection, suggesting that these TLRs and TLR-related molecules are not essential for host defense against that parasite [28]. A Th1 cytokine, IFN- γ , contributed to exacerbation of ECM development during *P. berghei* ANKA infection of IFN- γ R1-deficient (IFN- γ R1^{-/-}) mice [17], while Th17- and Th17-related cytokines such as IL-17 and IL-23 were not essential for development of ECM during this infection in IL-17^{-/-} mice or IL-23p19^{-/-} mice [6]. In addition, IL-4^{-/-} mice and IL-4R α ^{-/-} mice were resistant to infection with liver-stage sporozoites of *P. berghei* ANKA, but similarly susceptible to wild-type mice to infection with blood-stage parasites [22]. IgE^{-/-} mice and Fc ϵ R1 α ^{-/-} mice were also resistant to development of ECM during *P. berghei* ANKA infection [20]. In particular, Fc ϵ R1 α -expressing neutrophils, but not mast cells or basophils, were crucial for protection against *P. berghei* ANKA [20]. These observations suggest that Th1- and Th2-, but not Th17-, cytokines are important for host defense against *P. berghei* ANKA.

Epithelial cell-derived cytokines such as IL-25, IL-33 and TSLP were reported to contribute to induction of Th2-type immune responses such as host defense against helminth infection and allergic diseases by inducing Th2 cytokine production by various types of cells such as Th2 cells, mast cells, basophils and group 2 innate lymphoid cells (ILC2) [8,29,31]. Those findings suggested that all and/or each of them might be involved in host defense against *P. berghei* ANKA. Indeed, it was reported that the level of IL-33 was elevated in the plasma from children (under 5 years old) infected with *P. falciparum* [1]. In addition, it was recently reported that C57BL/6 mice treated with recombinant IL-33 showed prolonged survival and delayed parasitemia after *P. berghei* ANKA infection [2], suggesting that IL-33 has a protective role against *P. berghei* ANKA infection. On the other hand, it was also reported that mice lacking ST2, which is a component of IL-33 receptor, were resistant to ECM, but developed parasitemia normally, during *P. berghei* ANKA infection [18]. Those findings suggest that IL-33/ST2 signaling exacerbates ECM development, but does not contribute to parasitemia, in the setting. Thus, the role of IL-33 in host defense against *P. berghei* ANKA remains controversial. In addition, the contributions of IL-25 and TSLP to the pathogenesis of malaria parasite infection are not fully understood. Therefore, in the present study, we investigated the roles of IL-25, IL-33 and TSLP in the pathogenesis of malaria (*P. berghei* ANKA) infection by using IL-25^{-/-}, IL-33^{-/-} and TSLP receptor (TSLPR)^{-/-} mice.

2. Material and methods

2.1. Mice and parasites

BALB/c- and C57BL/6-wild-type mice were purchased from Japan SLC (Shizuoka, Japan). IL-25^{+/-} mice were obtained by mating male chimeric mice—which were generated by Lexicon Pharmaceuticals, Inc. using *il25*-targeted 129 ES cells (OYC069)—with C57BL/6J female mice (N8) [7]. C57BL/6-IL-33^{-/-} mice and BALB/c-TSLPR^{-/-} were generated as described elsewhere [3,14,15]. Female mice were used in all experiments. The mice were housed under specific-pathogen-free conditions at The Institute of Medical Science, The University of Tokyo. The animal protocol was approved by the Institutional Review Board of the Institute, and the study was conducted in accordance with the ethical and safety guidelines of the Institute (A11-29).

2.2. Parasite infection

Murine malaria parasite, *P. berghei* ANKA strain, was kindly gifted by Drs. Chris Janse and Andrew Waters (Leiden University, Leiden, the Netherlands). Parasites were propagated in female BALB/c mice by intraperitoneal injection as described elsewhere [24]. After injection, mice were monitored daily until death.

2.3. Real-time RT-PCR

Total RNA was extracted from the brains, livers, lungs and spleens of infected mice at the indicated time points, and reverse-transcribed to cDNA. The expression levels of IL-25, IL-33 and TSLP mRNA were quantified by SYBR Green dye incorporation assay using StepOnePlus real-time PCR system (Applied Biosystems, Carlsbad, CA). The expression levels of them were normalized to the expression levels of β -actin mRNA in individual samples. Data show the relative values against 0 DPI (=1). The PCR primers used were as follows: 5'-GGCATTCTACTCAGGAACGGA-3' and 5'-GGTGAGAAAGTGCTGTGC-3' for IL-25; 5'-TCCAACCCAA-GATTCCCG-3' and 5'-CATGCAGTAGACATGGCAGAA-3' for IL-33; 5'-CAATCCTATCCCTGGCTGCC-3' and 5'-TGTGCCATTTCCTGAG-TACCGT-3' for TSLP; and 5'-TCTACAATGAGCTGCGTGTGG-3' and 5'-TACAGGGACAGCACAGCCTGG-3' for β -actin.

2.4. Determination of parasitemia

Blood smears were made from tail blood of mice at the times indicated and fixed with methanol before staining with Giemsa. Parasitemia was quantified by counting the percentage of infected RBCs under microscopic observation.

2.5. Statistical analysis

Real-time RT-PCR data are shown as the mean with SEM and were evaluated using a two-tailed unpaired Student's *t*-test. Parasitemia data are shown as the mean with SEM and were evaluated for statistical significance using one-way analysis of variance (ANOVA). Survival of the mice after infection was analyzed by the Kaplan–Meier method, and *p*-values were calculated by the log-rank test. *P* < 0.05 was considered statistically significant.

3. Results and discussion

First, we examined the expression levels of IL-25, IL-33 and TSLP mRNA in brain, liver, lung and spleen tissues from C57BL/6-wild-type mice on days 2, 4 and 6 after injection of erythrocytes

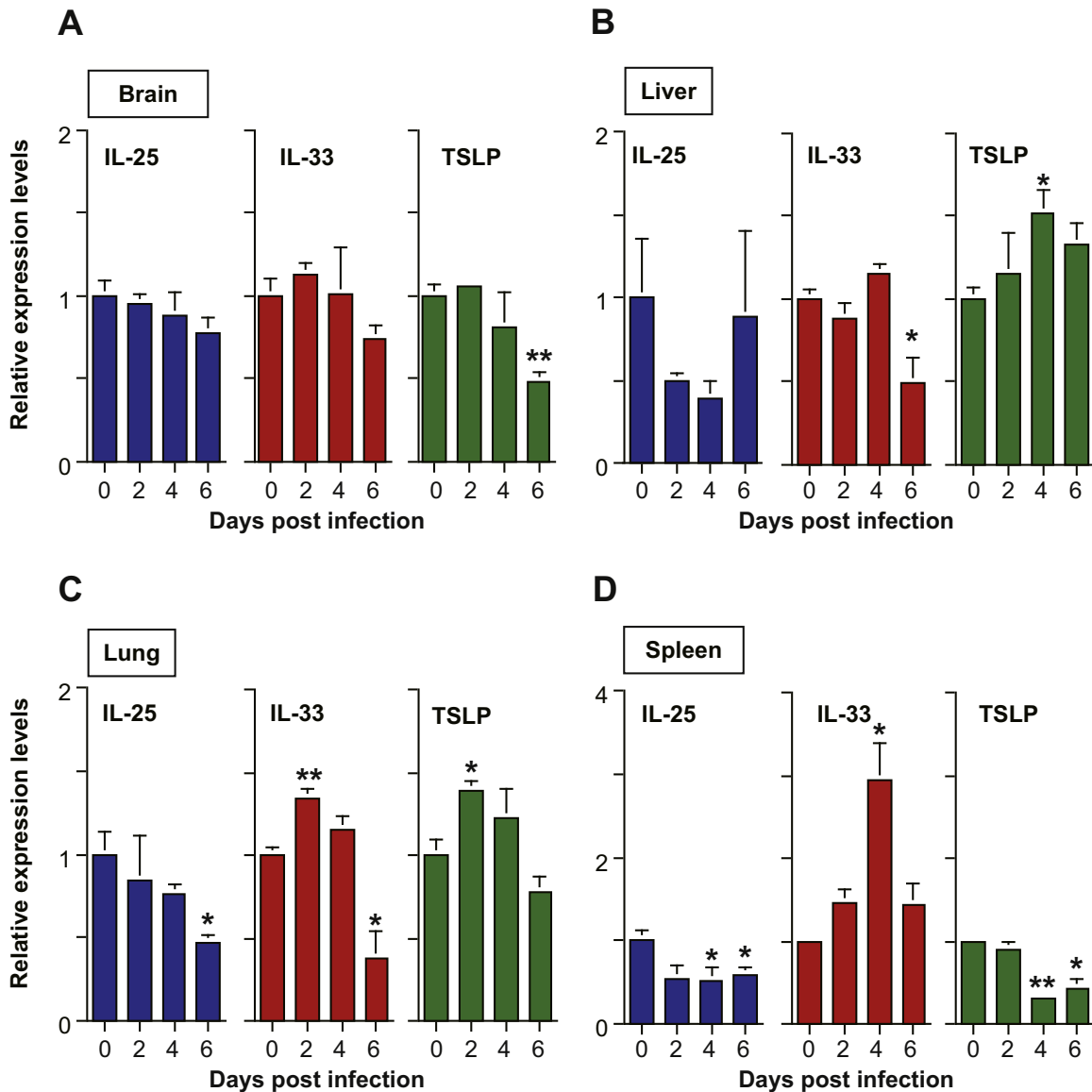


Fig. 1. Kinetics and levels of IL-25, IL-33 and TSLP mRNA expression in the brain, liver, lung and spleen of C57BL/6 wild-type mice during *P. berghei* ANKA infection. C57BL/6 wild-type mice were injected intraperitoneally with erythrocytes infected with *P. berghei* ANKA (1×10^5 infected erythrocytes/mouse). Total RNA was isolated from the brain, liver, lung and spleen of the mice at 0 (=naïve), 2, 4 and 6 days post-infection. The expression levels of IL-25, IL-33 and TSLP mRNA in these tissues were determined by quantitative PCR. The expression level of each mRNA was normalized to those of β -actin mRNA in individual samples. Data show the mean \pm SEM ($n=5$). * $p < 0.05$ and ** $p < 0.01$ vs. 0 day post-infection (=naïve mice).

infected with *P. berghei* ANKA (1×10^5 infected erythrocytes/mouse) (Fig. 1).

In the brain, the expression levels of IL-25 and IL-33 mRNA at 2, 4 and 6 days post-infection (DPI) were unaltered compared with at 0 DPI (=non-infected mice) (Fig. 1A). The brain expression levels of TSLP mRNA were also not changed at 2 and 4 DPI, but they were significantly decreased at 6 DPI, compared with at 0 DPI (Fig. 1A). These observations suggest that TSLP, but not IL-25 or IL-33, may be involved in development of ECM during *P. berghei* infection.

In the liver, the expression levels of IL-25, IL-33 and TSLP mRNA at 2, 4 and 6 DPI, at 2 and 4 DPI and at 2 and 6 DPI, respectively, were comparable to at 0 DPI (Fig. 1B). However, the liver expression levels of IL-33 mRNA at 6 DPI were significantly decreased compared with at 0 DPI (Fig. 1B), while TSLP mRNA at 6 DPI was significantly increased compared with at 0 DPI (Fig. 1B). These observations suggest that IL-33 and TSLP may be involved in induction of hepatic disorders caused by malaria parasite infection.

In the lung, the expression levels of IL-25 mRNA gradually

decreased time-dependently and were significantly reduced at 6 DPI compared with at 0 DPI (Fig. 1C). In contrast, the lung expression levels of IL-33 mRNA were significantly up-regulated at 2 DPI and then significantly reduced at 6 DPI compared with at 0 DPI (Fig. 1C). Likewise, the lung expression levels of TSLP mRNA were significantly up-regulated at 2 DPI, and then gradually, but not significantly, reduced at 6 DPI compared with at 0 DPI (Fig. 1C). These results suggest that IL-25, IL-33 and TSLP may be involved in the development of pulmonary inflammation accompanied by edema, in which monocytes and neutrophils accumulated following malaria parasite infection [23,27].

In the spleen, the expression levels of IL-25 and TSLP mRNA were significantly reduced at 4 and 6 DPI compared with those at 0 DPI (Fig. 1D), while the expression levels of IL-33 mRNA were significantly up-regulated at 4 DPI. These results suggest that IL-25, IL-33 and TSLP may somehow contribute to activation of immune cells in the spleen in the early stage of malaria parasite infection.

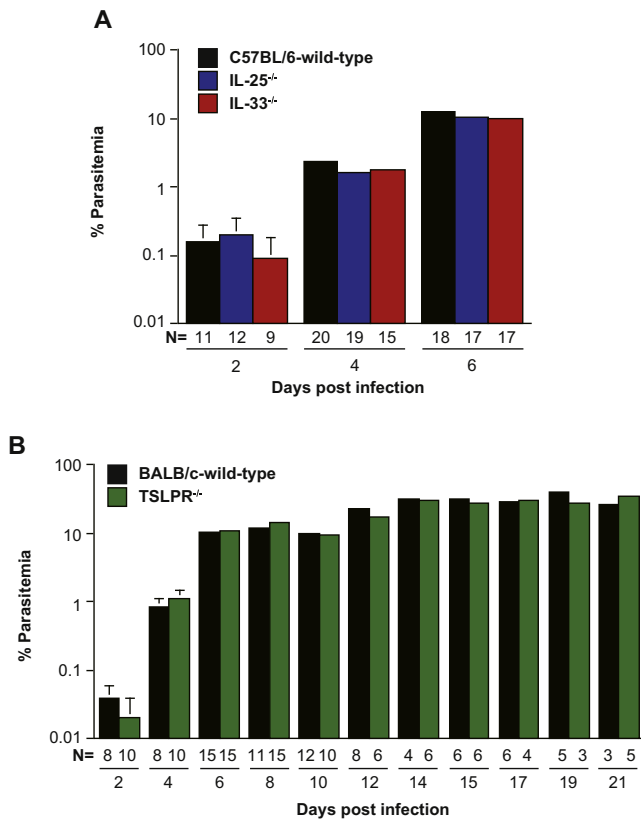


Fig. 2. Incidence of parasitemia in wild-type, IL-25^{-/-}, IL-33^{-/-} and TSLPR^{-/-} mice during *P. berghei* ANKA infection. Mice were injected intraperitoneally with erythrocytes infected with *P. berghei* ANKA (1×10^5 infected erythrocytes/mouse). Blood smears were made from tail blood of mice at the times indicated. (A) Wild-type mice, IL-25^{-/-} mice and IL-33^{-/-} mice on the C57BL/6 background. (B) Wild-type mice and TSLPR^{-/-} mice on the BALB/c background. Data show the mean \pm SEM and are representative of two or three separate, reproducible results. N: number of mice in the experimental group.

In order to elucidate whether these cytokines affected the parasitemia and survival rate after *P. berghei* infection, wild-type mice, IL-25^{-/-} mice and IL-33^{-/-} mice on the C57BL/6 background, and wild-type mice and TSLPR^{-/-} mice on the BALB/c background, were infected with *P. berghei*.

The development of parasitemia was comparable among the wild-type mice, IL-25^{-/-} mice and IL-33^{-/-} mice on the C57BL/6 background (Fig. 2A) and in the wild-type mice and TSLPR^{-/-} mice on the BALB/c background (Fig. 2B). These findings indicate that IL-25, IL-33 and TSLP were not essential for the development of parasitemia during *P. berghei* ANKA infection.

The survival rates were also comparable among the wild-type mice, IL-25^{-/-} mice and IL-33^{-/-} mice on the C57BL/6 background (Fig. 3A) and in wild-type mice and TSLPR^{-/-} mice on the BALB/c background (Fig. 3B) during *P. berghei* ANKA infection. These findings indicate that IL-25, IL-33 and TSLP were not essential for host defense against *P. berghei* ANKA. Histological analysis of brains revealed that the experimental cerebral malaria in the mutants was comparable to that in the wild-type mice (data not shown).

Infection of C57BL/6 mice with *P. berghei* ANKA (1×10^5 infected erythrocytes/mouse) resulted in early death due to cerebral malaria-like symptoms, caused mainly by an inflammatory cytokine storm [5,25]. Although BALB/c mice were more resistant to that same level of infection than the C57BL/6 mice, they also experienced early death due to the same symptoms and cause [5,25]. Thus, although the immune responses during *P. berghei* ANKA infection were not completely identical between C57BL/6 mice and

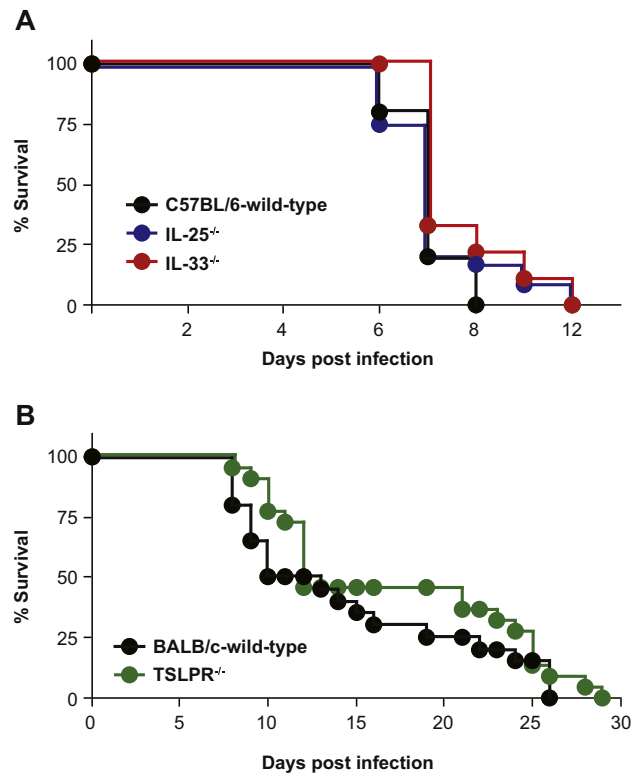


Fig. 3. Survival of wild-type, IL-25^{-/-}, IL-33^{-/-} and TSLPR^{-/-} mice during *P. berghei* ANKA infection. Mice were injected intraperitoneally with erythrocytes infected with *P. berghei* ANKA (1×10^5 infected erythrocytes/mouse). After injection, survival was monitored daily. (A) Wild-type mice ($n=10$), IL-25^{-/-} mice ($n=12$) and IL-33^{-/-} mice ($n=9$) on the C57BL/6 background. (B) Wild-type mice ($n=20$) and TSLPR^{-/-} mice ($n=22$) on the BALB/c background. Data show the mean \pm SEM and are representative of two or three separate, reproducible results.

BALB/c mice, we clearly demonstrated that IL-25, IL-33 and TSLP are not essential for host defense against *P. berghei* ANKA in both mouse lines, despite the finding that the pattern of mRNA expression for these cytokines was altered in various tissues such as the brain, liver, lung and spleen from the infected mice.

Like IL-33R (ST2)^{-/-} mice [18], IL-33^{-/-} mice normally developed parasitemia and pulmonary alterations during *P. berghei* ANKA infection. ST2^{-/-} mice were resistant to ECM during *P. berghei* ANKA infection [18], whereas IL-33^{-/-} mice showed normal susceptibility to it. The reason for this apparent difference between ST2^{-/-} mice and IL-33^{-/-} mice during *P. berghei* ANKA infection is unclear, but it was shown that the pathogenic phenotypes of IL-33^{-/-} mice did not correspond with those of ST2^{-/-} mice in regard to certain immune responses such as ovalbumin-induced airway inflammation [10,11,14,15] and collagen-induced arthritis [26,30]. Since it was reported that full-length IL-33 can induce inflammation independently of ST2 [9], IL-33 and/or ST2 may have alternative receptor(s) and/or ligand(s).

In summary, we elucidated the relationships between the pathogenesis of murine malaria parasite infection and IL-25, IL-33 and TSLP for the first time using IL-25^{-/-}, IL-33^{-/-} and TSLPR^{-/-} mice. Although the mRNA expression of IL-25, IL-33 and TSLP was changed in the brain, liver, lung and spleen of *P. berghei* ANKA-infected mice, these cytokines were not critical for host defense against *P. berghei* ANKA.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.bbrep.2015.12.007>.

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