Biochemical and Biophysical Research Communications 453 (2014) 1–6

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Potential role of myeloid cell/eosinophil-derived IL-17 in LPS-induced endotoxin shock

Eri Shimura [a], Akiko Shibui [b], Seiko Narushima [c], Aya Nambu [c], Sachiko Yamaguchi [c], Aoi Akitsu [d], Warren J. Leonard [e], Yoichiro Iwakura [d], Kenji Matsumoto [f], Hajime Suto [a], Ko Okumura [a], Katsuko Sudo [g], Susumu Nakae [c,h,*]

[a] Atopy Research Center, Juntendo University, Tokyo 113-8412, Japan
[b] Department of Medical Genomics, Graduate School of Frontier Sciences, The University of Tokyo, Chiba 277-8561, Japan
[c] Laboratory of Systems Biology, Center for Experimental Medicine and Systems Biology, The Institute of Medical Science, The University of Tokyo, Tokyo 108-8639, Japan
[d] Division of Experimental Animal Immunology, Tokyo University of Science, Chiba 278-8510, Japan
[e] Laboratory of Molecular Immunology and the Immunology Center, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD 20892, USA
[f] Department of Allergy and Immunology, National Research Institute for Child Health and Development, Tokyo 157-8535, Japan
[g] Animal Research Center, Tokyo Medical University, Tokyo 160-8402, Japan
[h] Precursory Research for Embryonic Science and Technology (PRESTO), Japan Science and Technology Agency, Saitama 332-0012, Japan

ARTICLE INFO

Article history:
Received 18 August 2014
Available online 6 September 2014

Keywords:
IL-17A
IL-17F
IL-25
Sepsis

ABSTRACT

IL-17RA is a shared receptor subunit for several cytokines of the IL-17 family, including IL-17A, IL-17C, IL-17E (also called IL-25) and IL-17F. It has been shown that mice deficient in IL-17RA are more susceptible to sepsis than wild-type mice, suggesting that IL-17RA is important for host defense against sepsis. However, it is unclear which ligands for IL-17RA, such as IL-17A, IL-17C, IL-17E/IL-25 and/or IL-17F, are involved in the pathogenesis of sepsis. Therefore, we examined IL-17A, IL-17E/IL-25 and IL-17F for possible involvement in LPS-induced endotoxin shock. IL-17A-deficient mice, but not IL-25- or IL-17F-deficient mice, were resistant to LPS-induced endotoxin shock, as compared with wild-type mice. Nevertheless, studies using IL-6-deficient, IL-21Rα-deficient and Rag-2-deficient mice, revealed that neither IL-6 and IL-21, both of which are important for Th17 cell differentiation, nor Th17 cells were essential for the development of LPS-induced endotoxin shock, suggesting that IL-17A-producing cells other than Th17 cells were important in the setting. In this connection, IL-17A was produced by macrophages, DCs and eosinophils after LPS injection. Taken together, these findings indicate that IL-17A, but not IL-17F or IL-25, is crucial for LPS-induced endotoxin shock. In addition, macrophages, DCs and eosinophils, but not Th17 cells or γδ T cells, may be sources of IL-17A during LPS-induced endotoxin shock.

1. Introduction

To date, at least six cytokines, i.e., interleukin-17 (IL-17, also called IL-17A), IL-17B, IL-17C, IL-17D, IL-17E (also called IL-25) and IL-17F, and five cytokine receptor proteins, i.e., IL-17RA, IL-17RB, IL-17RC, IL-17RD and IL-17RE, have been identified as members of the IL-17 cytokine and IL-17R receptor families, respectively [1,2]. IL-17A and IL-17F bind to IL-17R (composed of IL-17RA and IL-17RC), IL-17C binds to IL-17CR (composed of IL-17RA and IL-17RE) and IL-25 binds to IL-25R (composed of IL-17RA and IL-17RB) [3]. However, the receptors for IL-17B and IL-17D have not been fully elucidated, although IL-17B is known to bind to IL-17RB [4]. Thus, excluding IL-17B and IL-17D, IL-17RA is considered to be a shared receptor subunit for many IL-17 cytokines, including IL-17A, IL-17C, IL-17F and IL-25.

Administration and/or overexpression of IL-17A, IL-17B, IL-17C, IL-17D and/or IL-17F in mice resulted in development of neutrophilic inflammation by inducing neutrophil chemoattractants [5–7], and this contributed to host defense against various pathogens [8]. On the other hand, administration and/or overexpression of IL-25 in mice resulted in development of eosinophilic inflammation by inducing Th2 cytokines such as IL-4, IL-5 and IL-13 [9–11], which contributed to host defense against nematodes [12–14]. However, inappropriate and excessive production of these cytokines is also

* Corresponding author at: Laboratory of Systems Biology, Center for Experimental Medicine and Systems Biology, The Institute of Medical Science, The University of Tokyo, 4-6-1 Shirokanedai, Minato, Tokyo 108-8639, Japan. Fax: +81 3 6409 2109.
E-mail address: snakae@ims.u-tokyo.ac.jp (S. Nakae).

http://dx.doi.org/10.1016/j.bbrc.2014.09.004
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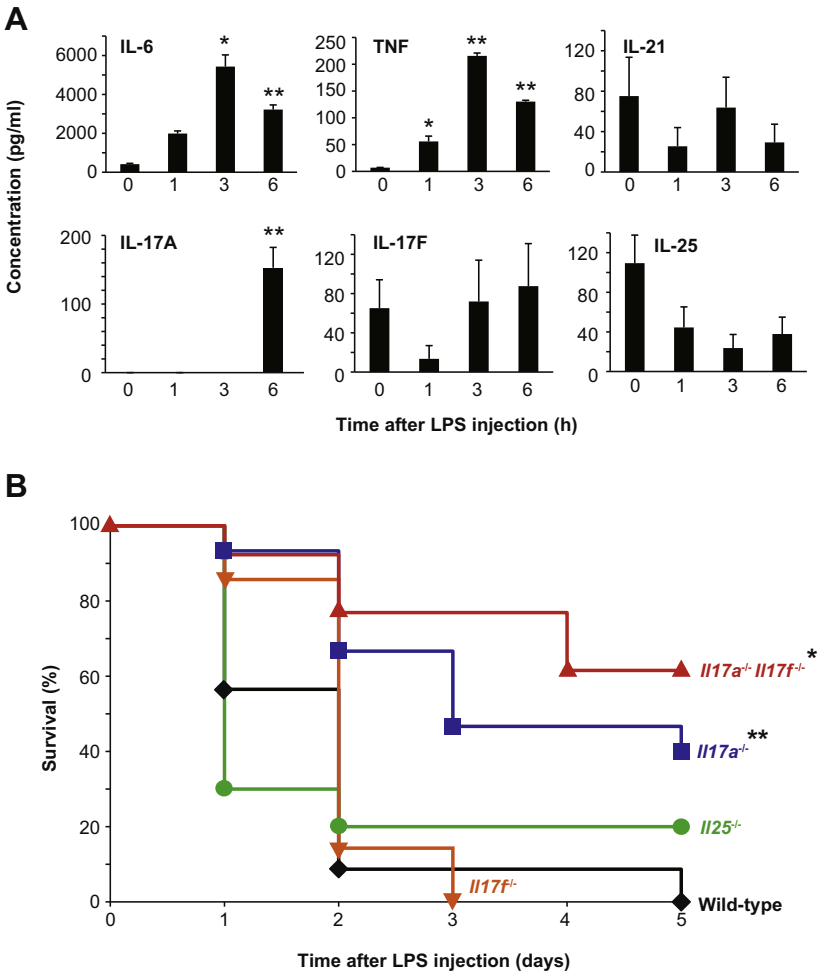

Fig. 1. IL-17A, but not IL-17F or IL-25, is important for LPS-induced endotoxin shock. (A) C57BL/6J-wild-type mice were intraperitoneally injected with LPS (15 mg/kg), and peritoneal lavage fluids were collected. The concentrations of IL-17A, IL-17E, IL-17F, IL-6, IL-21 and TNF in the fluids were measured by ELISA. Data show the mean ± SEM. $N = 10$ (0 h), 4 (1 h), 9 (3 h) and 10 (6 h). $^{*}p < 0.05$ and $^{**}p < 0.005$ vs. 0 h. (B) Wild-type mice ($n = 27$), IL-17A$^{-/-}$ mice ($n = 14$), IL-17F$^{-/-}$ mice ($n = 11$), IL-17A$^{-/-}$ IL-17F$^{-/-}$ mice ($n = 10$) and IL-25$^{-/-}$ mice ($n = 12$) on the C57BL/6J background were intraperitoneally injected with LPS (10 mg/kg). The viability of these mice was monitored daily. Data show pooled data from 2 independent experiments. $^{*}p < 0.001$ and $^{**}p < 0.005$ vs. wild-type mice.

involved in development of chronic inflammatory diseases such as autoimmune and allergic diseases [1,15]. In particular, inappropriate and/or excessive IL-17A or IL-17F, which are produced by various types of cells, such as Th17 cells, γδ T cells, iNKT cells, NK cells and/or LTi cells [16,17], contributes to development of rheumatoid arthritis, multiple sclerosis, inflammatory bowel diseases, psoriasis, asthma and/or contact dermatitis [1]. IL-17A and IL-17F may also be involved in induction of acute inflammation such as sepsis. Indeed, the IL-17A and IL-17F levels were increased in mice with sepsis induced by caecal ligation and puncture (CLP) [18–20]. In addition, mice treated with neutralizing Ab for IL-17A were resistant to sepsis induced by CLP, suggesting that IL-17A, especially γδ T cell-derived IL-17A, promotes sepsis [18]. In contrast, IL-17A-deficient (*Il17a*$^{-/-}$) mice were more susceptible to sepsis induced by CLP than wild-type mice, suggesting that IL-17A helps protect against sepsis [21]. Therefore, the role(s) of IL-17A in the development of sepsis following CLP remains controversial. In addition, like the *Il17a*$^{-/-}$ mice [21], *Il17ra*$^{-/-}$ mice were also more susceptible to CLP-induced sepsis than wild-type mice [22]. Because, as noted above, IL-17RA is a shared receptor subunit for IL-17A, IL-17C, IL-17F and IL-25, it was unclear if the *Il17ra*$^{-/-}$ phenotype of mice was due solely to the lack of IL-17A during sepsis, or whether defective signaling by IL-17C, IL-17F, or IL-25 might also contribute. Therefore, in the present study, we used *Il17a*$^{-/-}$, *Il17f*$^{-/-}$, *Il17a*$^{-/-}$ *Il17f*$^{-/-}$ and *Il25*$^{-/-}$ mice to investigate the roles of IL-17A, IL-17F and IL-25 in sepsis induced by LPS injection. We found that IL-17A, but not IL-17F or IL-25, produced by macrophages was crucial for LPS-induced endotoxin shock.

2. Materials and methods

2.1. Mice

C57BL/6J wild-type mice were purchased from SLC Japan. *Il17a*$^{-/-}$, *Il17f*$^{-/-}$, and *Il17a*$^{-/-}$ *Il17f*$^{-/-}$ mice on the C57BL/6J background were generated as described elsewhere [23,24]. *Il25*$^{+/-}$ 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) [25]. IL-17A-green fluorescent protein (GFP) reporter mice were generated by Y.I. (unpublished). C57BL/6-*Rag2*$^{-/-}$ mice and C57BL/6-*Il6*$^{-/-}$ mice were obtained from Taconic Farm and Jackson Laboratories, respectively. C57BL/6J-*Il21ra*$^{-/-}$ mice were generated as described elsewhere [26]. Eight- to 12-wk-old male mice were used in all experiments. All mice were housed under specific pathogen-free conditions in an environmentally-controlled clean room at The Institute of Medical Science, The University of Tokyo. All animal experiments were approved by the Institutional Review Board

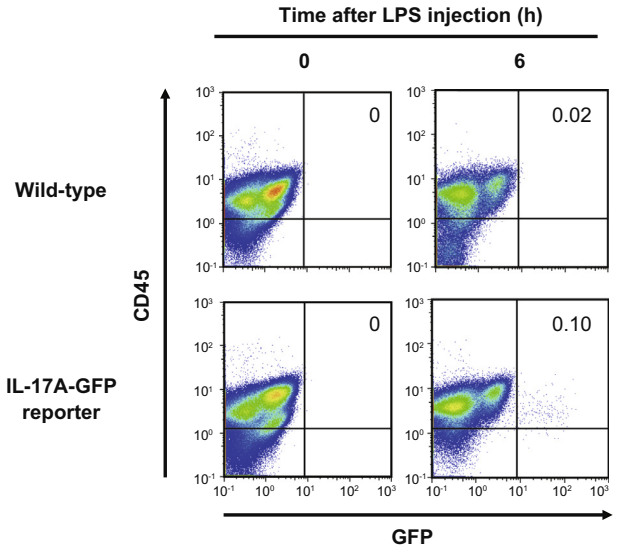

Fig. 2. Detection of IL-17A-producing cells in peritoneal lavage fluids of mice after intraperitoneal LPS injection. IL-17A-EGFP reporter mice were intraperitoneally injected with 15 mg/kg LPS, and peritoneal lavage fluids were collected 6 h later. IL-17A-producing EGFP$^+$ cells in 7-aminoactinomycin D-negative CD45$^+$ peritoneal cells were detected by flow cytometry. Data show a representative result from 4 independent experiments.

of The Institute of Medical Science, The University of Tokyo, and conducted in accordance with the ethical and safety guidelines of the institution (A20-12).

2.2. LPS-induced endotoxin shock

Mice were intraperitoneally injected with 10–15 mg/kg of LPS (*Escherichia coli* serotype 0111:B4; Sigma–Aldrich). After LPS injection, the survival of the mice was monitored for 5 days.

2.3. Preparation of peritoneal cells

Six hours after LPS injection, mice were intraperitoneally injected with 2 ml of PBS. Peritoneal cells were then collected in the peritoneal lavage fluids from the mice.

2.4. Measurement of cytokines

The concentrations of IL-6, IL-17A, IL-17F, IL-21, IL-25, IL-6, and TNF in the peritoneal lavage fluids from LPS-injected mice were measured using ELISA kits (eBioscience or BioLegend), according to the manufacturer's instructions.

2.5. Flow cytometry analysis

Peritoneal cells were incubated with anti-CD16/CD32 mAb (93, eBioscience) in FACS buffer (phosphate-buffered saline containing 1% inactivated fetal calf serum and 0.1% NaN_3) for 15 min on ice and then incubated with PE-conjugated anti-mouse CD45R/B220 (RA3-6B2; BD Bioscience), PE/Cy7-conjugated anti-mouse CD11b (M1/70; BD Bioscience), BD Horizon V500 anti-mouse CD3ε (500A2; BD Bioscience), APC-conjugated anti-mouse F4/80 (BM8; BioLegend) and APC/Cy7-conjugated anti-mouse CD11c (N418; BD BioLegend) mAbs for 25 min on ice. After washing, the cells were suspended in FACS buffer containing 7-amino actinomycin D, and determined with a MACSQuant (Miltenyi Biotec), and analyzed with FlowJo software (Tree Star).

2.6. Statistical analysis

The Kaplan–Meier method using the log-rank test was used for statistical evaluation of animal survival. Unless otherwise specified, the unpaired Student's *t*-test, two-tailed, was used for statistical evaluation of the results.

3. Results

3.1. IL-17A, but not IL-17F or IL-25, is important for LPS-induced endotoxin shock

Proinflammatory cytokines such as TNF are known to be important for the pathogenesis of LPS-induced endotoxin shock [27]. Indeed, the levels of TNF as well as IL-6 increased rapidly and significantly in the peritoneal fluids of C57BL/6 wild-type mice after LPS injection (Fig. 1A). The levels of IL-17A, but not IL-17F, IL-25 or IL-21, were also increased in the setting (Fig. 1A), suggesting that IL-17A may be involved in LPS-induced endotoxin shock.

To clarify this, we injected LPS intraperitoneally to mice deficient in IL-17A, IL-17F or IL-25. As shown in Fig. 1B, *Il17a*$^{-/-}$ mice as well as *Il17a*$^{-/-}$ *Il17f*$^{-/-}$ mice were resistant to LPS-induced endotoxin shock compared with wild-type mice. On the other hand, *Il17f*$^{-/-}$ mice showed susceptibility similar to that of wild-type mice for LPS-induced endotoxin shock, whereas the effect in *Il25*$^{-/-}$ mice was intermediate (Fig. 1B). These observations indicate that IL-17A, rather than IL-17F or IL-25, is the most important of these cytokines for induction of endotoxin shock by LPS.

3.2. Myeloid cells and eosinophils, but not Th17 cells, are a source of IL-17A during LPS-induced endotoxin shock

To identify the types of cells producing IL-17A during LPS-induced endotoxin shock, we injected LPS intraperitoneally into IL-17A reporter mice, which express EGFP simultaneously with IL-17A. Six hours later, EGFP-positive CD45$^+$ cells were observed in the peritoneal fluids (Fig. 2). Furthermore, the CD45$^+$ EGFP$^+$ cells were identified as TCRβ$^+$ and TCRγ$^+$ CD3ε$^+$ CD4$^+$ T cells, but not CD3$^+$ CD8$^+$ T cells or TCRβ$^+$ CD3$^+$ DX5/CD49d$^+$ cells (Fig. 3A), suggesting that Th17 cells and γδ T cells, but not CD8$^+$ T cells or NKT cells, are potential sources of IL-17A in the setting. In addition, Siglec F$^+$ CD11b$^+$ cells (eosinophils), MHC class II$^{hi/int}$ F4/80$^{hi/int}$ cells (monocytes/macrophages), MHC class II$^+$ CD11c$^+$ cells (DCs) and B220$^+$ CD19$^+$ cells (B cells), but not CD11b$^+$ Gr1$^+$ cells (neutrophils) were identified as producers of IL-17A (Fig. 3B). Therefore, in addition to Th17 cells and γδ T cells, eosinophils, macrophages, DCs and B cells are also potential sources of IL-17A during LPS-induced endotoxin shock.

Th17 cells, which differentiate from naïve CD4$^+$ T cells in the presence of TGF-β, IL-6 and/or IL-21 [28], are known to be a major source of IL-17A and IL-17F [28]. Consistent with a previous report [29], *Il6*$^{-/-}$ mice showed similar death to WT mice by day 4, although they may have slightly be better survival at earlier time points. *Il21ra*$^{-/-}$ mice also had similar survival to wild-type mice, but interestingly, *Il6*$^{-/-}$ *Il21*$^{-/-}$ mice if anything had more severe disease, with all animals succumbing by day 3 (Fig. 4A). These observations suggest that IL-6 and IL-21R are not essential for IL-17A-mediated LPS-induced endotoxin shock. In addition, in contrast to *Il17a*$^{-/-}$ mice (Fig. 1B), *Rag2*$^{-/-}$ mice, which lack T cells, B cells and NKT cells, were more highly susceptible to LPS-induced endotoxic shock than wild-type mice were (Fig. 4B), suggesting that such cells are important for suppression of LPS-induced endotoxin shock. Taken together, these findings suggest that IL-17A derived from macrophages, DCs and/or eosinophils, but not T cells, B cells or NKT cells, is crucial for induction of LPS-induced endotoxin shock.

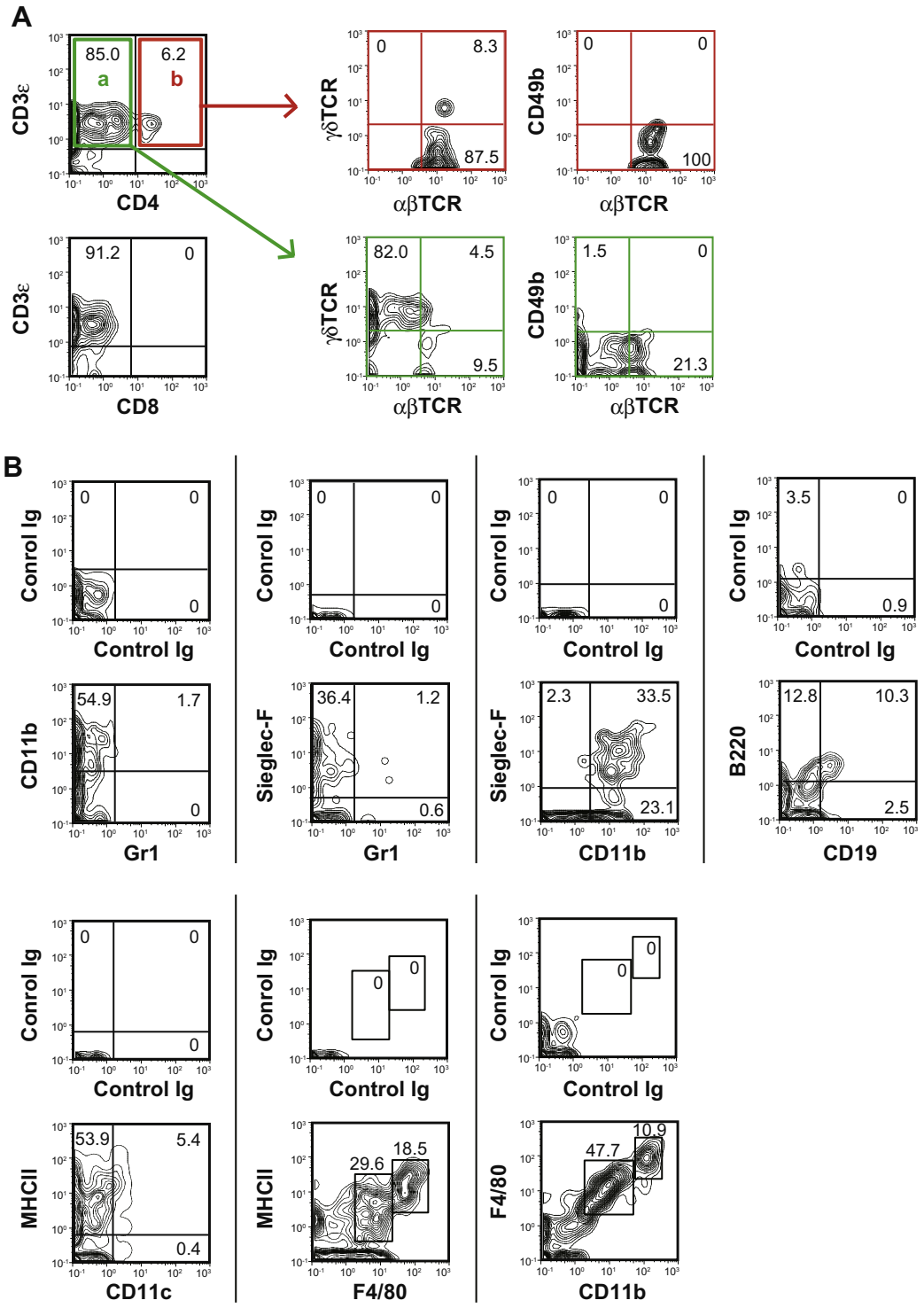

Fig. 3. Identification of IL-17A-producing cells in peritoneal lavage fluids of mice after intraperitoneal LPS injection. Cell lineage markers on the 7-aminoactinomycin D-negative CD45$^+$ EGFP$^+$ peritoneal cells obtained from the LPS-injected IL-17A-EGFP reporter mice described in Fig. 3 were determined by flow cytometry. (A) T cell subsets and NKT cells. (B) B cells, neutrophils, eosinophils, macrophages and dendritic cells. Data show a representative result from 3 independent experiments.

4. Discussion

Il17ra$^{-/-}$ mice were reported to be more susceptible to sepsis induced by CLP compared with wild-type mice [22], suggesting involvement of ligands for IL-17RA, such as IL-17A, IL-17C, IL-17F and IL-25, in induction of sepsis. On the other hand, the role of IL-17A to induction of sepsis by CLP has been controversial. That is, mice treated with neutralizing Ab for IL-17A were resistant [18], but *Il17a*$^{-/-}$ mice were susceptible [21], to sepsis induced by CLP. Therefore, it is unclear which ligand(s) for IL-17RA is crucial for the response. In the present study, we show that *Il17a*$^{-/-}$ mice were resistant, but *Il17f*$^{-/-}$ mice and *Il25*$^{-/-}$ mice were normally susceptible, to LPS-induced endotoxin shock. That suggests that IL-17A, but not IL-17F or IL-25, is an important effector

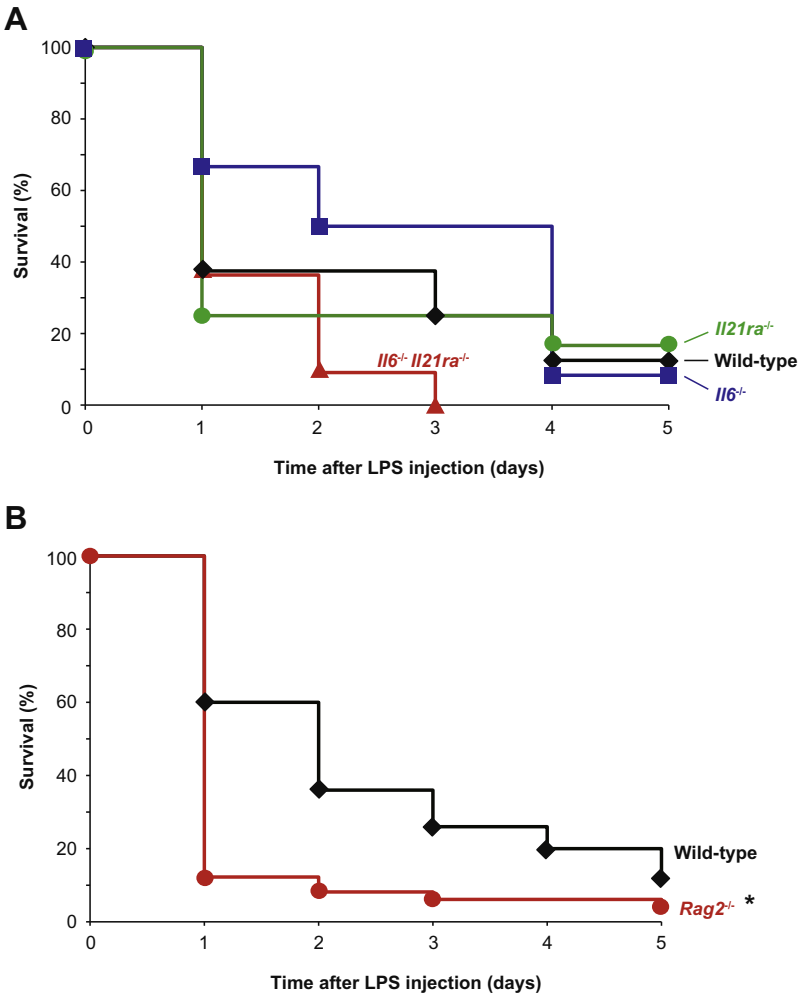

Fig. 4. IL-6 and IL-21Rα are dispensable for LPS-induced endotoxin shock. (A) Wild-type mice ($n = 12$), IL-6$^{-/-}$ mice ($n = 16$), IL-21Rα$^{-/-}$ mice ($n = 14$) and IL-6$^{-/-}$ IL-21Rα$^{-/-}$ mice ($n = 15$) on the C57BL/6J background were intraperitoneally injected with LPS (15 mg/kg). (B) Wild-type mice ($n = 50$), and Rag-2$^{-/-}$ mice ($n = 52$) on the C57BL/6J background were intraperitoneally injected with LPS (15 mg/kg). The viability of these mice was monitored daily. Data show pooled data from 2 independent experiments. $^{*}p < 0.05$ vs. wild-type mice.

cytokine for LPS-induced endotoxin shock, although it should be noted that the pathogenic mechanism of the LPS-induced and CLP-induced sepsis models is not exactly the same [30].

We also found that macrophages, DCs and eosinophils—but not T cells (such as Th17 cells, CD8^{+} T cells and γδ T cells), B cells or NKT cells—were potential sources of IL-17A in LPS-induced endotoxin shock. Although it was reported that γδ T-cell-derived IL-17A may contribute to aggravation of CLP-induced sepsis [18], the contributions of T cells and B cells to induction of sepsis are controversial. In this regard, while it was reported that T cells, especially regulatory T cells (Treg cells), and B cells were important for protection against CLP-induced or microbe-induced sepsis [31,32], others reported that these cells were not involved in CLP-induced sepsis [33,34]. We showed that IL-17A was rapidly expressed in Th17 cells, γδ T cells, B cells, macrophages and eosinophils, but not in CD8^{+} T cells, NKT cells or neutrophils, in IL-17A reporter mice after intraperitoneal LPS injection. However, IL-6 and IL-21, which are important for the development of Th17 cells, were not essential for LPS-induced endotoxin shock. In addition, *Rag2*$^{-/-}$ mice, which lack T cells, B cells and NKT cells, were more highly susceptible to LPS-induced endotoxin shock, while *Il17a*$^{-/-}$ mice were resistant to it. These observations suggest that T cells, B cells and/or NKT cells play protective roles against LPS-induced endotoxin shock. Therefore, although IL-17 is important for the development of LPS-induced endotoxin shock, Th17 cell- and γδ T cell-derived IL-17 does not appear to be required.

In summary, IL-17A, but not IL-17F or IL-25, is crucial for LPS-induced endotoxin shock. In addition, macrophages, DCs and eosinophils, but not Th17 cells or γδ T cells, may be sources of that IL-17A during LPS-induced endotoxin shock.

Acknowledgments

We thank Wakako Nakanishi, Yoshihisa Hiraishi, Ayano Yamauchi-Ishii, Tsubasa Sato and Hiromi Iwami for their technical assistance. We also thank Lawrence W. Stiver (Tokyo, Japan) for his critical reading of the manuscript. This work was supported by Grants-in-Aid for Young Scientists (B) (E.S.), Grants-in-Aid for Young Scientists (A) (S. Nakae) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Health Labour Sciences Research Grants from the Ministry of Health, Labour and Welfare, Japan (K.M.), The Grant of National Center for Child Health and Development (23A-5) (K.M.), and Precursory Research for Embryonic Science and Technology, Japan Science and Technology Agency (S. Nakae.). W.J.L. was supported by the Division of Intra-mural Research, National Heart, Lung, and Blood Institute, NIH, Bethesda, MD.

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