Interleukin-17A during Local and Systemic Staphylococcus aureus-Induced Arthritis in Mice

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Staphylococcus aureus is one of the dominant pathogens that induce septic arthritis in immunocompromised hosts, e.g., patients suffering from rheumatoid arthritis treated with immunosuppressive drugs. S. aureus-induced arthritis leads to severe joint destruction and high mortality despite antibiotic treatment. Recently, interleukin-17A (IL-17A) has been discovered to be an important mediator of aseptic arthritis both in mice and humans, but its function in S. aureus-induced arthritis is largely unknown. Here, we investigated the role of IL-17A in host defense against arthritis following systemic and local S. aureus infection in vivo. IL-17A knockout mice and wild-type mice were inoculated systemically (intravenously) or locally (intra-articularly) with S. aureus. During systemic infection, IL-17A knockout mice lost significantly more weight than the wild-type mice did, but no differences were found in the mortality rate. The absence of IL-17A had no impact on clinical arthritis development but led to increased histopathological erosivity late during systemic S. aureus infection. Bacterial clearance in kidneys was increased in IL-17A knockout mice compared to the level in wild-type mice only 1 day after bacterial inoculation. During systemic S. aureus infection, serum IL-17F protein levels and mRNA levels in the lymph nodes were elevated in the IL-17A knockout mice compared to the level in wild-type mice. In contrast to systemic infection, the IL-17A knockout mice had increased synovitis and erosions and locally decreased clearance of bacteria 3 days after local bacterial inoculation. On the basis of these findings, we suggest that IL-17A is more important in local host defense than in systemic host defense against S. aureus-induced arthritis.

Patients with rheumatoid arthritis (RA) are susceptible to bacterial joint infections as a result of immunosuppressive treatments and the disease per se (24). The most common agent causing joint infections is Staphylococcus aureus, a microbe that can also cause sepsis. S. aureus-induced arthritis is a severe problem with a mortality rate of 5 to 20%, and 25 to 70% of affected patients develop permanent joint damage despite treatment (24). Although substantial efforts have been made to understand the immunological mechanisms that lead to S. aureus-induced joint destruction, it remains difficult to treat the infection (by maintaining the host’s ability to clear bacteria) while simultaneously limiting the joint destruction (by suppressing the immunological response). Thus, there is a need to identify new ways to treat RA that do not increase the severity of S. aureus-induced arthritis following infection.

Recent evidence from humans and mice suggesting that the proinflammatory cytokine interleukin-17A (IL-17A) is an important player in RA (3, 19, 21) prompted an ongoing clinical trial of IL-17A-blocking antibodies to treat RA (6). Interleukin-17A was first described in 1993, but it was not until 2005, when Harrington et al. (8) described the unique Th17 subset, that the relevance of this cytokine was widely recognized among immunologists (5, 13, 15). Interleukin-17A appears to play a key role in host defense against local Gram-negative extracellular bacterial infections (4, 7, 9, 10, 17, 22, 29, 30) and local S. aureus infections (18) by inducing the production of neutrophil-mobilizing chemokines and growth factors and the subsequent mobilization of neutrophils (5, 13, 15, 16). Importantly, Ishigame et al. have recently shown that genetical knockout of IL-17A plus IL-17F (double knockout) in mice has very little impact on the general outcome of systemic S. aureus infection, measured as mortality and bacterial clearance at a single time point after bacterial inoculation compared with wild-type mice (11). However, in this study, the respective roles of IL-17A and -17F in S. aureus-induced arthritis were not specifically addressed (11), and this aspect is the main focus of this study. S. aureus-induced arthritis is a great concern in RA (24), and the first phase I study using IL-17A-blocking antibodies as a treatment in RA has recently been published (6). Thus, it is clinically important to determine whether reduced IL-17A levels in RA patients would have a detrimental effect on S. aureus-induced arthritis.

It is well-known that, within the IL-17 family, IL-17F is the cytokine that shares the greatest structural and functional homology with IL-17A (5, 15). Both IL-17A and IL-17F exist as homodimers or as IL-17A–IL-17F heterodimers and bind to the IL-17 receptor A (IL-17RA)–IL-17RC receptor complex (28). Furthermore, these three IL-17 cytokines may exert similar biological effects, in particular with reference to the local mobilization of neutrophils (23). Studies of healthy mice have also shown that IL-17A is capable of inhibiting the production of bacterial clearance at a single time point after bacterial inoculation compared with wild-type mice (11). Therefore, it is clinically important to determine whether reduced IL-17A levels in RA patients would have a detrimental effect on S. aureus-induced arthritis.

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of IL-17F under certain conditions, through a IL-17RA-dependent mechanism (27). Thus, IL-17A and IL-17F seem to be functionally linked. In the present study, we characterized the kinetics of systemic and local S. aureus infections in the presence and absence of IL-17A in mice. For this purpose, we used IL-17A knockout mice (21) and wild-type control mice in our well-established mouse models of systemic and local S. aureus-induced arthritis (1) and assessed specific aspects of arthritis and more-general clinical outcomes. Using this approach, we obtained evidence that bacterial clearance, cytokine pattern, and degree of arthritis vary over time during systemic S. aureus infection and that IL-17A plays a more important role in local host defense than in systemic host defense against S. aureus-induced arthritis.

MATERIALS AND METHODS

Mice. Both male and female C57BL/6J and BALB/c IL-17A knockout mice (20) were used. The mice were genotyped by PCR using HotStarTaq master kit (Qiagen, Solna, Sweden) with the following primers: common primer (5′ ACT CTT CAT CCA CCT CAG AGG A 3′), wild-type primer (5′ GTA CAC CAG CTA TCC TGC AGA TAG 3′), and mutant primer (5′ GCC ATG ATA TAG AGC TGG TGG C 3′). The hypoxanthine-guanine phosphoribosyltransferase (HPRT) housekeeping gene was used as a control. Wild-type C57BL/6J and BALB/c mice were from Scabur (Sollentuna, Sweden). The mice were bred and maintained (10 mice in each cage) under standard conditions of temperature and light in the animal facility at the Department of Rheumatology and Inflammation Research, University of Gothenburg, Sweden. Permission from the local Animal Research Ethics Committee, in accordance with national animal welfare legislation, was obtained for all the experiments.

Mouse model of systemic S. aureus-induced arthritis. It has previously been shown that toxic shock syndrome toxin 1 (TSST-1) enhances IL-17A production in vitro from human peripheral blood mononuclear cells (2, 12). In this study, we used the TSST-1-producing LS-1 strain of S. aureus for infection. IL-17A knockout mice (n = 67) and wild-type mice (n = 71) with a C57BL/6J background were inoculated intravenously (i.v.) in the tail vein with 0.2 × 10^6 to 1 × 10^6 S. aureus LS-la bacteria/mouse in a total volume of 200 μl phosphate-buffered saline (PBS). IL-17A knockout mice (n = 12) and wild-type mice (n = 12) with a BALB/c background were inoculated i.v. with 0.8 × 10^5 S. aureus LS-1 bacteria/mouse in a total volume of 200 μl PBS. Viable-cell counts were performed to determine the number of bacteria injected. The mice were killed 3 days later. One knee joint was taken for histological examination, and the synovial membrane from the other knee was taken for bacterial examination, fluorescence-activated cell sorting (FACS), and analysis of myeloperoxidase (MPO) content.

Bacterial examination of the synovial membrane. The synovial membrane was aseptically dissected, kept on ice, centrifuged at 500 × g for 10 min, and resuspended in 2 ml of Luria-Bertani (LB) medium. After 24 h of incubation with stirring at 37°C, the solution was serially diluted in PBS and spread on blood agar plates. The number of CFU was determined after 24 h of incubation at 37°C. In addition, the synovial membrane was aseptically dissected, melted in 100 μl PBS, and spread on blood agar plates, and the presence or absence of CFU was determined after 24 h of incubation at 37°C.

Single-cell preparation of synovial cells. The synovial membrane was aseptically dissected, kept on ice, centrifuged at 500 × g for 10 min, and incubated in 1 ml of RPMI 1640 medium containing 10% heat-inactivated fetal calf serum (FCS) (Sigma-Aldrich AB, Stockholm, Sweden), 1 mg/ml collagenase IV (Sigma-Aldrich AB), and 0.2 mg/ml DNase (Roche, Bromma, Sweden) for 1 h at 37°C. The synovial membranes were homogenized, passed through a nylon mesh (70 μm), and washed with RPMI 1640 medium containing 10% heat-inactivated fetal calf serum, and the number of cells was counted.

FACS of synovial cells. After a single-cell suspension had been prepared, the synovial cells from either IL-17 knockout mice (n = 4) or wild-type mice (n = 4) were resuspended in PBS containing 2% FCS, 1 mM EDTA, and 0.1% sodium azide (FACs buffer). The cells were counted and incubated with an optimal concentration of anti-CD45 (2.4G2) (BD Biosciences, San Jose, CA) for 8 min at 4°C to avoid nonspecific binding via Fc receptor interaction. To stain the cells, we used directly labeled antibodies, phycoerythrin (PE)-conjugated anti-Gr-1 (clone RB6-8C5) (BD Biosciences, San Jose, CA) and allophycocyanin-cyanine dye 7 (APC-Cy7)-conjugated anti-I-A/I-E (clone 114.15.2) (Biolegend, San Diego, CA). The cells were incubated with the antibodies for a minimum of 30 min at 4°C in the dark and then washed twice with FACS buffer. Pelleted cells were resuspended in FACS buffer and detected by using a FACSCanto II (BD Biosciences, San Jose, CA) and analyzed by FlowJo software (Tree Star Inc., Ashland, OR).

Determination of MPO content in the synovial cells. The MPO content in the synovial cells was measured as enzyme activity. After a single-cell suspension had been prepared, the cells were lysed for 1 h at room temperature in 20 μl of lysis buffer and counted. The degree of synovitis and erosion yielded a score from 0 to 3 in every joint concerning fingers/toes, wrists/ankles, elbows, and knees. Occasionally one paw was missing in the histological sections or embedded in a way that made it impossible to evaluate the degree of synovitis and bone/cartilage erosion, and therefore, the total score for a mouse is divided by the number of joints evaluated.

Examination of infected kidneys. The kidneys were aseptically dissected, kept on ice, homogenized, serially diluted in PBS, and spread on blood agar plates. The number of CFU per kidney pair was determined after 24 h of incubation at 37°C.

Measurement of cytokines. Blood samples were centrifuged at 7,000 × g for 10 min. Serum samples were collected and stored at −20°C for further analysis. The protein levels of IL-17A, IL-17F, and granulocyte-stimulating factor (G-CSF) were measured by a sandwich enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Europe Ltd., Abingdon, United Kingdom) according to the manufacturer’s recommendations and detected by using a Spectra Max 340PC (Molecular Devices, Sunnyvale, CA). Serum levels of IL-6, IL-10, monocyte chemotactic protein 1 (MCP-1), gamma interferon (IFN-γ), tumor necrosis factor (TNF), and IL-12p70 were measured using cytometric bead array (CBA) mouse inflammation kit (BD Biosciences, Erebodgem, Belgium). The assay was run on a FACS Canto II BD (BIOSciences).
buffer containing 0.2% cetrimonium bromide (CTAB) (Sigma-Aldrich AB) and 0.2% bovine serum albumin (BSA) (Sigma-Aldrich AB) in PBS. The peroxidase substrate 1,2-phenylenediamine dihydrochloride (OPD) (Dako, Stockholm, Sweden) was dissolved according to the manufacturer’s directions and mixed with H₂O₂ immediately before use. Forty microliters of peroxidase substrate was added to the samples and incubated for 1.5 h at room temperature. The absorbance was measured at 450 nm on a Spectra Max 340PC (Molecular Devices, Sunnyvale, CA).

Statistical analysis. Statistical analyses were performed using GraphPad Prism (La Jolla, CA). Statistical differences between independent groups were calculated using the nonparametric Mann-Whitney U test or Fisher’s exact probability test. Kaplan-Meier survival plots were prepared, and the log rank test was used to compare the two survival curves. A P value of <0.05 was considered statistically significant.

RESULTS

Systemic S. aureus-induced arthritis is not more severe in IL-17A knockout mice. Although the IL-17A knockout mice lost significantly more weight than the wild-type mice did 3, 9, and 11 days after intravenous S. aureus inoculation (Fig. 1A), the weight change was not due to a lower initial weight among the IL-17A knockout mice at the start of the experiment (Fig. 1B). There were no differences in mortality or in the severity or frequency of clinically assessed arthritis at any time point (Fig. 1C to E). To ensure that these results were not due to the mouse strain used (C57BL/6), we repeated the same experiments using mice with a BALB/c background, and similar results were obtained (Fig. 2A to C). Histological sections from the C57BL/6 strain 3 and 7 days after bacterial inoculation also showed that similar degrees of synovitis and erosivity developed in the IL-17A knockout mice and wild-type mice after intravenous bacterial inoculation (Fig. 1F). However, 13 days after bacterial inoculation, C57BL/6 IL-17A knockout mice displayed significantly more erosions than the wild-type mice did (Fig. 1F).

Clearance of bacteria from kidneys is increased in IL-17A knockout mice early during systemic S. aureus infection. Bacterial clearance from the kidneys of C57BL/6 mice was significantly higher in IL-17A knockout mice than in wild-type mice 1 day after S. aureus inoculation. At later time points, the values for bacterial clearance were similar in both groups of mice (Table 1). There were no differences in bacterial clearance at any time point in IL-17A knockout mice and wild-type mice with the BALB/c background (Table 1).

Serum levels of IL-17F, but not G-CSF or circulating neutrophils, are increased in IL-17A knockout mice during systemic S. aureus infection. Expression of IL-17F mRNA in lymph nodes was significantly higher in IL-17A knockout mice than in wild-type mice both before S. aureus inoculation and 13 days after S. aureus inoculation (Fig. 3A). Serum protein levels of IL-17F were significantly increased in IL-17A knockout mice 1, 7, and 13 days after infection (Fig. 3B). In contrast, there were no differences in serum protein levels of G-CSF or in the number of circulating neutrophils in blood in IL-17A knockout and wild-type mice (Fig. 3C and D). Similar results were obtained when IL-17A knockout mice with the BALB/c background were examined (Fig. 2D). IL-17A protein levels were barely detectable in serum from either strain of wild-type mice (data not shown).

Serum levels of IL-6 are decreased and serum levels of IFN-γ are increased in IL-17A knockout mice during systemic S. aureus infection. Serum protein levels of IL-6 were significantly decreased 13 days after S. aureus inoculation (Fig. 4A).
contrast, serum IFN-γ protein levels were significantly increased in IL-17A knockout mice compared to the levels in the wild-type mice 1 day after inoculation (Fig. 4B). We did not detect any differences in the serum protein levels of IL-10, MCP-1, TNF-α, or IL-12p70 in IL-17A knockout and wild-type mice (data not shown).

IL-17A knockout mice have more severe arthritis and reduced clearance of bacteria after local *S. aureus* infection. Intra-articular inoculation of *S. aureus* into the knee joint induced a significantly more severe synovitis and erosive arthritis in the IL-17A knockout mice than in the wild-type mice 3 days after inoculation (Fig. 5A to C). Bacterial growth was found in 3 of 5 IL-17A knockout mice compared with 1 of 5 wild-type mice when the synovial membrane was directly spread on a blood agar plate. In addition, to determine the number of bacteria per synovial membrane, a broth culture of the synovial membranes was performed, and the bacterial load was significantly increased in IL-17A knockout mice compared to the level in wild-type mice 3 days after intra-articular inoculation (Fig. 6A). There was a clear trend toward decreased numbers of neutrophils in the synovial membranes from the IL-17A knockout mice compared with wild-type mice (Fig. 6B and C), while the MPO activity was similar in both groups (Fig. 6D).

**DISCUSSION**

In this study, we investigated the importance of IL-17A in systemic or local *S. aureus* arthritis by using IL-17A knockout mice and wild-type mice. We found that the absence of IL-17A in the model of systemic *S. aureus* arthritis had no

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<th>TABLE 1. Recovery of bacteria from the kidneys of IL-17A knockout mice and wild-type mice inoculated i.v. with <em>S. aureus</em></th>
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<td><strong>No. of days after inoculation</strong></td>
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<td><strong>Wild-type</strong></td>
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*Two different strains of mice, C57BL/6 and BALB/c mice, were tested.*

*The results for the number of bacteria recovered from the kidneys are shown in colony-forming units, and the results are expressed as means ± standard errors of the means. The number of mice is shown in brackets. The asterisk indicates that this mean value was significantly different (*P* = 0.03) from the mean value for wild-type mice. ND, not done.*
marked impact on the overall mortality or on the clinical development of arthritis. Clearance of bacteria in kidneys was significantly increased in the IL-17A knockout mice early during systemic infection, which coincided with increased serum levels of IFN-γ in these mice. Interestingly, the IL-17A knockout mice had significantly higher expression of both mRNA (on day 13 only) and serum protein levels of IL-17F compared with the wild-type mice both before and after S. aureus inoculation. Importantly, these findings were not strain specific, since similar outcomes were seen in both C57BL/6 and BALB/c mice with respect to mortality, morbidity, development of arthritis, and IL-17F protein levels. In contrast to systemic infection, local S. aureus-induced arthritis caused a significantly more severe synovitis and destructive arthritis and locally impaired bacterial clearance in IL-17A knockout mice compared with wild-type mice.

The study by Ishigame et al. showed that IL-17A and IL-17F double knockout in mice does not influence the general outcome of systemic S. aureus infection, measured as mortality and bacterial clearance in kidneys at day 3 only, after bacterial inoculation compared with wild-type mice (11). In our current study, we characterized the kinetics of systemic S. aureus infection in IL-17A knockout mice and compared these mice with wild-type mice of the same strain (C57BL/6 and BALB/c), and we found that bacterial clearance, cytokine pattern, and...
degree of arthritis all vary over time during systemic *S. aureus* infection. Furthermore, Ishigame et al. showed that the IL-17A and IL-17F double knockout mice, but not IL-17A or IL-17F single knockout mice, have a significantly impaired bacterial clearance during spontaneous mucocutaneous infection which was caused by *S. aureus* (11). In the present study, we have clearly shown that 3 days after intra-articular inoculation of a defined TSST-1-producing *S. aureus* strain, the local bacterial burden is significantly increased and both synovitis and joint destruction are aggravated in the absence of IL-17A. These findings could be partly explained by a clear trend toward a lower number of neutrophils with retained MPO activity in IL-17A knockout mice. The differences between our current results and the results of Ishigame et al. (11) could be due to several factors, including differences in the anatomical sites of infection and duration of infection time and also possibly in the use of spontaneous infection which might *per se* include the involvement of additional bacterial strains and species. Collectively, our current data and previously published data (11, 18) suggest that IL-17A and IL-17F are involved in host defense against *S. aureus* infection but also that their relative importance varies depending on whether the infection is local or systemic, the anatomical site of the local infection, and the duration of infection.

In line with earlier studies showing that IL-17A and IL-17F mediate similar biological effects and that IL-17A inhibits IL-17F production (23, 27), we found that IL-17F mRNA was upregulated in IL-17A knockout mice even before systemic *S. aureus* infection.
S. aureus infection. We observed that IL-17F protein levels were increased 1, 7, and 13 days after infection. We believe that these findings are important, as they are compatible with a compensatory mechanism by which IL-17F can functionally replace IL-17A and maintain host defense against systemic staphylococcal infection, when IL-17A is lacking, at least during infections with short or medium duration. This particular finding warrants further investigations.

We also investigated the effect of IL-17A knockout on other cytokines known to play a role in bacterial clearance. Previous studies have shown that G-CSF increases neutrophil counts and thereby bacterial clearance (26). Both IL-17A and IL-17F are known to induce granulopoiesis through the production of G-CSF (23), and von Vieninghoff and Ley have shown that both IL-17F and G-CSF are increased in the absence of IL-17A in healthy, uninfected mice (27). In contrast, in our current study, we did not observe any change in either serum G-CSF levels or in blood neutrophil counts, but we did observe increased serum IL-17F protein levels in the IL-17A knockout mice than in the wild-type mice at any of the time points measured after systemic S. aureus infection. Collectively, these findings that are compatible with IL-17F maintaining G-CSF levels in the absence of IL-17A.

It is well-known that IL-17A inhibits IFN-γ in vivo. It is therefore intriguing that we found that systemic S. aureus inoculation led to increased levels of IFN-γ in serum 1 day after inoculation in the IL-17A knockout mice compared to the levels in the wild-type mice, which coincided with a significantly improved bacterial clearance in kidneys in the knockout mice. Later during this systemic S. aureus infection, we could not detect any differences either in IFN-γ levels or in bacterial clearance. Upon this basis, we speculate that long-term elevated protein levels of IL-17F and of IL-17A (25) might have clearance. Upon this basis, we speculate that long-term elevated IL-17F and G-CSF levels or in bacterial clearance during infection by increasing phagocytic activity in neutrophils and macrophages (31, 32). It is therefore intriguing that we found that systemic S. aureus inoculation led to increased levels of IFN-γ in serum 1 day after inoculation in the IL-17A knockout mice compared to the levels in the wild-type mice, which coincided with a significantly improved bacterial clearance in kidneys in the knockout mice. Later during this systemic S. aureus infection, we could not detect any differences either in IFN-γ levels or in bacterial clearance. Upon this basis, we speculate that long-term elevated protein levels of IL-17F and of IL-17A (25) might have clearance. Upon this basis, we speculate that long-term elevated IL-17F and G-CSF levels or in bacterial clearance during infection by increasing phagocytic activity in neutrophils and macrophages (31, 32). It is therefore intriguing that we found that systemic S. aureus inoculation led to increased levels of IFN-γ in serum 1 day after inoculation in the IL-17A knockout mice compared to the levels in the wild-type mice, which coincided with a significantly improved bacterial clearance in kidneys in the knockout mice. Later during this systemic S. aureus infection, we could not detect any differences either in IFN-γ levels or in bacterial clearance. Upon this basis, we speculate that long-term elevated protein levels of IL-17F and of IL-17A (25) might have clearance. Upon this basis, we speculate that long-term elevated IL-17F and G-CSF levels or in bacterial clearance during infection by increasing phagocytic activity in neutrophils and macrophages (31, 32). It is therefore intriguing that we found that systemic S. aureus inoculation led to increased levels of IFN-γ in serum 1 day after inoculation in the IL-17A knockout mice compared to the levels in the wild-type mice, which coincided with a significantly improved bacterial clearance in kidneys in the knockout mice. Later during this systemic S. aureus infection, we could not detect any differences either in IFN-γ levels or in bacterial clearance. Upon this basis, we speculate that long-term elevated protein levels of IL-17F and of IL-17A (25) might have clearance. Upon this basis, we speculate that long-term elevated IL-17F and G-CSF levels or in bacterial clearance during infection by increasing phagocytic activity in neutrophils and macrophages (31, 32). It is therefore intriguing that we found that systemic S. aureus inoculation led to increased levels of IFN-γ in serum 1 day after inoculation in the IL-17A knockout mice compared to the levels in the wild-type mice, which coincided with a significantly improved bacterial clearance in kidneys in the knockout mice. Later during this systemic S. aureus infection, we could not detect any differences either in IFN-γ levels or in bacterial clearance. Upon this basis, we speculate that long-term elevated protein levels of IL-17F and of IL-17A (25) might have clearance. Upon this basis, we speculate that long-term elevated IL-17F and G-CSF levels or in bacterial clearance during infection by increasing phagocytic activity in neutrophils and macrophages (31, 32). It is therefore intriguing that we found that systemic S. aureus inoculation led to increased levels of IFN-γ in serum 1 day after inoculation in the IL-17A knockout mice compared to the levels in the wild-type mice, which coincided with a significantly improved bacterial clearance in kidneys in the knockout mice. Later during this systemic S. aureus infection, we could not detect any differences either in IFN-γ levels or in bacterial clearance. Upon this basis, we speculate that long-term elevated protein levels of IL-17F and of IL-17A (25) might have clearance. Upon this basis, we speculate that long-term elevated IL-17F and G-CSF levels or in bacterial clearance during infection by increasing phagocytic activity in neutrophils and macrophages (31, 32). It is therefore intriguing that we found that systemic S. aureus inoculation led to increased levels of IFN-γ in serum 1 day after inoculation in the IL-17A knockout mice compared to the levels in the wild-type mice, which coincided with a significantly improved bacterial clearance in kidneys in the knockout mice.


