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Aryl hydrocarbon receptor protects against *viridans streptococci* infection by activation of immune system through IL-17RA signaling

Guowei Liang[1], David Lazenby[1], Jonathan D Groden[1], Xing Liu[2], Suzan N Pretlow[1], Mark H Mertens[1*]

Abstract

The majority of bacterial infections during neutropenia following high-dose chemotherapy or stem cell transplantation are caused by coagulase-negative staphylococci, a large number are due to *viridans streptococci*. Despite considerable progress in the understanding of the AhR-mediated regulation of immune responses, the role of AhR in bacterial infections has not been clearly demonstrated. In the study presented here, we sought to determine whether the aryl hydrocarbon receptor (AhR) would protect mice from infection with *viridans streptococci*. AhR enhances the inflammatory response to *viridans streptococci* stimuli. Specifically, neutrophil numbers and levels of inflammatory cytokines are often increased in mice treated with *viridans streptococci*. Furthermore, AhR activation through the IL-17RA is required for protection against viridans streptococcal infection. Taken together, we concluded that AhR plays an important role in optimal innate immunoprotection against microbial infection through the down-regulation of immune response.

Keywords: *Viridans streptococcal*; AhR; Inflammatory cytokines; IL-17RA

*Corresponding author email: MarkH@gmail.com
[1]Center for Environmental Genetics, University of Cincinnati Medical Center, USA
[2]Osaka City University, Medical School, Japan
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Introduction

There is considerable evidence that signaling through the aryl hydrocarbon receptor (AHR) alters the course of adaptive immune responses in a manner that can be protective or detrimental. Adaptive immune responses underlie host protection from pathogens, but when improperly controlled they contribute to numerous diseases [1].

The AHR's remarkable capacity to modulate T cell responses has been demonstrated in autoimmune diseases1–5, allergic inflammation [2] , and inflammatory bowel diseases [3]. Yet, these reports also suggest that different AHR ligands may bias adaptive immune responses in opposite directions, and that exposure to the same ligand can worsen or improve pathology in different disease models [4].

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While these issues remain to be resolved, the ability of the AHR to modulate T cell differentiation and T cell-dependent immune responses has generated enthusiasm about targeting therapeutic agents at the AHR in order to modulate the progression of a large spectrum of immune-mediated diseases [5].

Yet, there is another aspect of AHR immunobiology that has direct bearing on the potential success of new strategies to use AHR ligands as treatment modalities: the impact on host responses to infection. Several reports demonstrate the importance of AHR in sensing microbes, including pathogenic and commensal bacteria, mycobacteria, and fungi [6]. Epidemiological studies show strong correlations between exposure to anthropogenically-derived AHR ligands from the environment and increased incidence and severity of respiratory infections, most notably viral infections [7].

These observations have been extended with animal studies, showing that AHR modulates cell-mediated and humoral immune responses to infection, and subsequently disease outcome [8]. A limitation of current information about AHR effects on adaptive immune responses during infection is that much of this evidence stems from studies conducted when AHR is activated using the high affinity binding environmental contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), which is resistant to metabolism. This raises questions about whether other compounds that bind AHR will similarly dampen key host protective adaptive immune responses to infection [9].

We report here a side-by-side comparison of the *in vivo* consequences of treatment with four different agonists on the adaptive immune response to infection with influenza A virus (IAV). To represent AHR binding compounds from different sources, we used 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), 3,3′,4,4′,5-pentachlorobiphenyl-126 (PCB126), 2-(1*H*-Indol-3-ylcarbonyl)-4-thiazolecarboxylic acid methyl ester (ITE), and 6-formylindolo(3,2-b)carbazole (FICZ). TCDD is the prototype and best characterized AHR ligand [10].

PCB126 is an abundant environmental contaminant with documented human exposure, yet its effects on the immune system remain understudied [11]. ITE represents pharmaceutical agents because of its potent AHR agonist activity *in vitro* and *in vivo*25–27, FICZ is a degradation product of tryptophan, and represents a naturally derived AHR ligand [12]. Infection with IAV elicits a vigorous adaptive immune response that involves virus-specific CD8+ cytotoxic T lymphocytes (CTL), conventional and regulatory CD4+ T cells, and virus-specific antibodies32,33. The overall magnitude of the adaptive response to IAV generally predicts the outcome following infection32,34,35. Using these four compounds, we compared CD8+ T cell, CD4+ T cell, and antibody responses to mild acute primary IAV infection.

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Methods and Material

Mice and bacteria

C57BL/6 wild-type (WT) mice. AhR KO mice (C57BL/6 background) have been described previously [13]. All the mice were maintained under specific pathogen-free conditions. LM was cultured in brain–heart infusion (BHI) broth with 50 μg/ml streptomycin. Heat-killed LM (HKLM) was prepared by incubation of mid-log bacteria at 80°C for 3h followed by three washes with sterile PBS.

In vivo experiments

Six-week-old AhR KO mice and littermate WT mice were infected i.p. with the indicated dose of LM. Organs and peritoneal macrophages were lysed/homogenized with lysis buffer solution (sterile water containing 0.2% Triton X-100). Organ/cell lysates were diluted *ad libitum* and plated onto BHI agar plates containing 50 μg/ml streptomycin. After incubation at 37°C, the colony-forming unit (CFU) per organ or macrophages were counted.

Cytokine and AIM ELISA

The cells were infected with the indicated dose of LM for 24h. Mouse IL-6, TNF-α and IL-10 from either the supernatant or the serum were measured by ELISA, according to the manufacturer's instructions (R&D Systems). Mouse AIM from the supernatant was measured by ELISA, according to the manufacturer's instructions (CycLex).

Western blot analysis

Peritoneal macrophages and RAW cells were infected with the indicated dose of LM for the indicated times. Cells were lysed with a lysis buffer [1% NP-40, 20mM Tris-HCl (pH 7.5), 150mM NaCl, 10mM Na_2VO_4, 0.5mM dithiothreitol, 1/100 protease inhibitor cocktail] and then subjected to SDS–PAGE. Whole cell lysates were analyzed with western blotting using anti-AhR (BIOMOL International) or anti-cleaved Caspase-3 (Cell Signaling).

Luciferase assay

RAW cells were transfected with 1 μg of the reporter plasmid and, in cotransfection experiments, with 0.1 μg of pRL-TK for use as an internal control reporter. Cells were infected with LM at a multiplicity of infection (MOI) of 1 for 12h and lysed with luciferase lysis reagent (Promega). Luciferase activity was determined with a commercial Dual-Luciferase reporter assay system (Promega) according to the manufacturer's instructions. Relative light units of Firefly luciferase activity were normalized with Renilla luciferase activity.

Cell death assays

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Peritoneal macrophages and RAW cells were infected with the indicated dose of LM for 24h. For the lactate dehydrogenase (LDH) release assay, culture supernatant was collected after infection and cell death was quantified using a cytotoxicity detection kit according to the manufacturer's instructions (Roche). For the cell imaging assay, cells were stained with a LIVE/DEAD Cell Imaging kit, according to the manufacturer's instructions (Molecular Probes) and imaged on Keyence BZ-9000 to determine whether they were live (green) or dead (red). Using an MEBCYTO Apoptosis Kit (MBL), cells were washed in PBS and re-suspended in 100 μl of binding buffer.

Cells were then incubated with 10 μl of annexin V-FITC for 15min at room temperature in the dark, followed by the addition of 400 μl of binding buffer and analysis using a BD FACSCanto II. For the cytotoxicity assay, cells were seeded 24h before the assay in 96-well plates at a density of 2×10^5 cells per well. Cells were treated with the indicated dose of pyocyanin in the presence or absence of AIM. After treatment for 24h, cell viability was assessed with a Cell Counting Kit (Dojin Laboratories, Kumamoto, Japan).

RT–PCR and quantitative real-time PCR

Total RNA was prepared using RNeasy (Qiagen), and cDNA was prepared as described in elsewhere [14-16]. Quantitative real-time PCR was performed using the primers in combination with SsoFast EvaGreen Supermix (Bio-Rad, Hercules, CA, USA) by a CFX384 real-time PCR detection system (Bio-Rad). The expression level of glyceraldehyde 3-phosphate dehydrogenase (G3PDH) was evaluated as an internal control. The specific primers for quantitative real-time PCR were as follows: $p40^{phox}$, sense 5′-GCCGCTATCGCCAGTTCTAC-3′ and anti-sense 5′-GCAGGCTCAGGAGGTTCTTC-3′; G3PDH, sense 5′-AACTTTGGCATTGTGGAAGG-3′ and anti-sense 5′-GGATGCAGGGATGATGTTCT-3′.

Statistical analysis

Student's *t*-test was used to analyze data for significant differences. Values of $P < 0.05$ were regarded as significant.

Results

AhR KO mice are highly susceptible to LM infection

Although previously shown that AhR deficiency enhanced the bacterial burden, they did not investigate the mortality of AhR KO mice after LM infection [17]. To clearly demonstrate the role of AhR in host-protective responses in vivo, we first treated AhR KO mice and littermate WT mice with various doses of LM. All AhR KO mice died within 3 and 5 days of infection with 5×105 and 1×105 CFU, respectively (Fig. 1A), which indicates that AhR KO mice are highly susceptible to LM infection compared with WT mice. Next, AhR KO and WT mice were i.p. infected with 1×105 CFU of LM, and the bacterial burdens in the spleen and liver were

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measured after 2 days. LM counts in each organ of AhR KO mice were higher than those in WT mice (Fig. 1B).

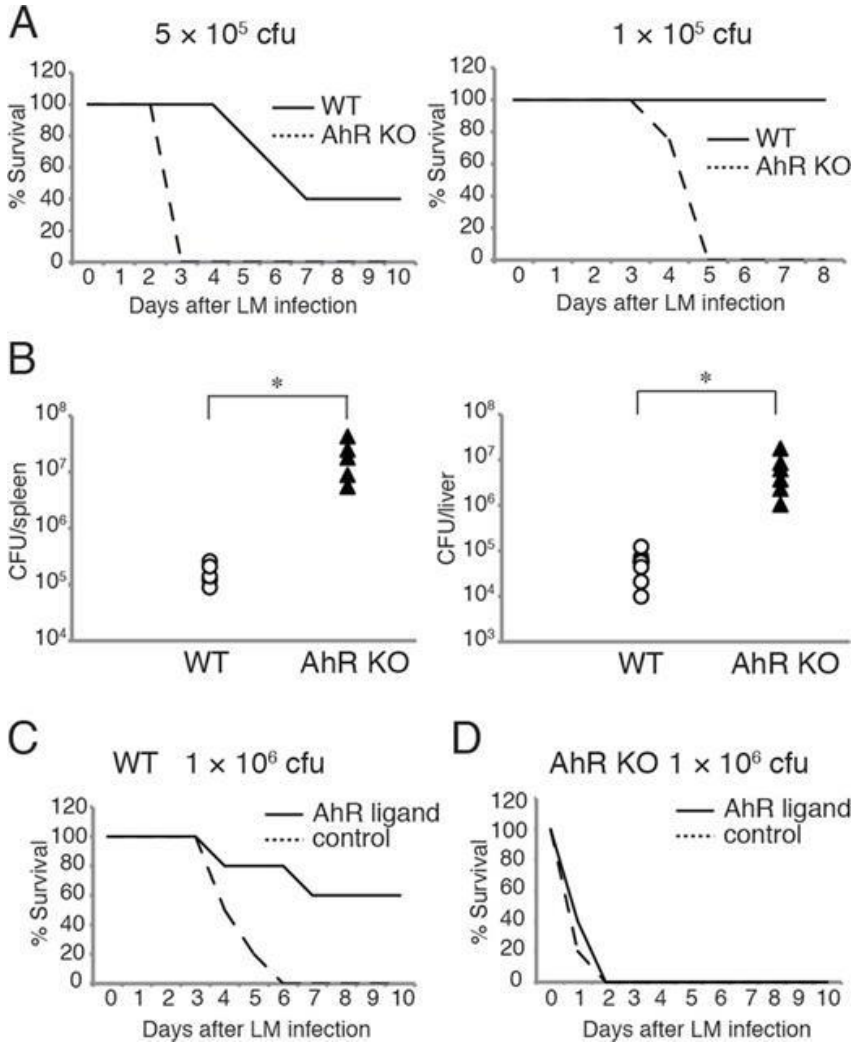

Figure 1.

Enhanced mortality in AhR KO mice after LM infection. Six- to eight-week-old AhR KO mice and littermate WT mice were infected i.p. with 5×10^5 CFU, 1×10^5 CFU (A and B) or 1×10^6 CFU (C and D) of LM. (A) Lethality was observed over 8 days after LM treatment. Data are representative of three independent experiments. (B) Bacterial load in spleen and liver was determined at 2 days post-infection. Data are representative of three independent experiments (*$P < 0.05$). (C and D) WT mice and AhR KO mice were infected i.p. with 1×10^6 CFU of LM. FICZ (100 μg/kg) was injected i.p. daily. Lethality was observed over 10 days after LM treatment with or without FICZ. Data are representative of three independent experiments.

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AhR deficiency results in the hyperactivation of macrophages during LM infection in vitro

AhR is induced by various stimuli in various types of immune cells [17]. To determine whether AhR is induced in macrophages infected with LM, peritoneal macrophages were challenged with LM, and AhR expression was measured by western blotting. AhR protein was induced in peritoneal macrophages infected with LM (Fig. 2A). Next, we examined the effect of AhR on the production of cytokines during LM infection. As shown in Fig. 2(B), IL-6 and TNF-α were induced after LM infection, and those levels were significantly higher in AhR KO peritoneal macrophages than in WT cells. In contrast, the production of anti-inflammatory cytokine IL-10 was reduced in LM-infected AhR KO macrophages (Fig. 2C).

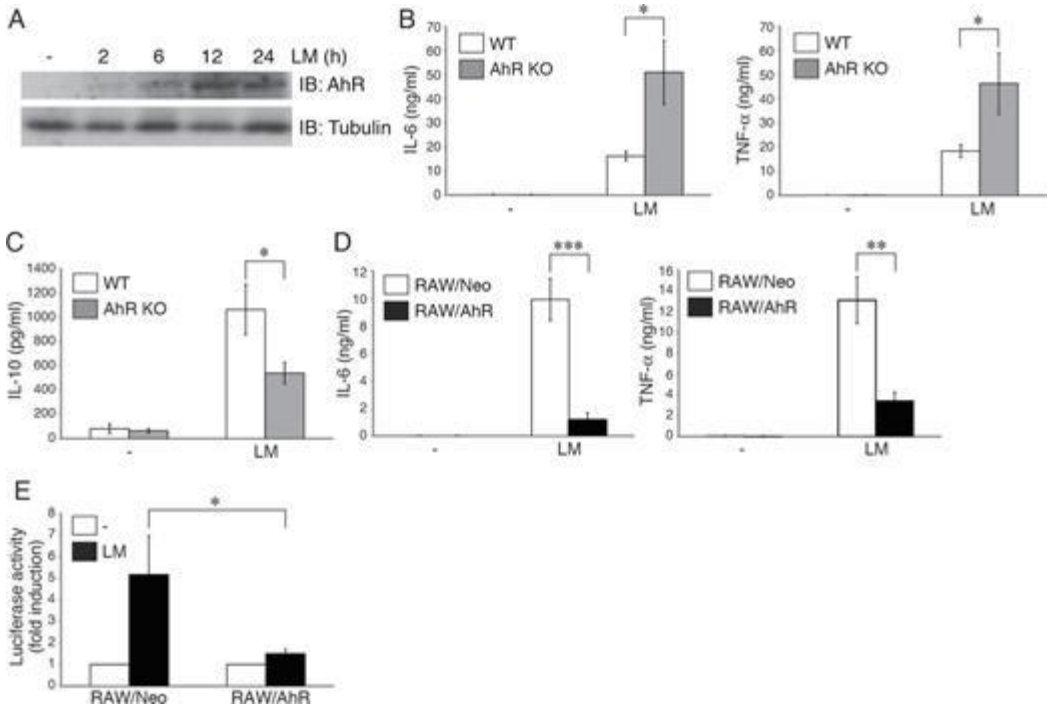

Figure 2.

Enhanced pro-inflammatory responses in AhR-deficient macrophages after LM infection. (A) Peritoneal macrophages were infected with LM for 24h. The cells were lysed and subjected to immunoblotting analysis for the expression of AhR and tubulin. IB denotes immunoblot. (B and C) WT and AhR-deficient macrophages were infected with LM at an MOI of 1. Supernatant was collected 24h after infection and the production of IL-6, TNF-α (B) and IL-10 (C) was measured by ELISA. Data show means ± SEM (*P < 0.05). (D) RAW/Neo and RAW/AhR cells were infected with LM at an MOI of 1. Supernatant was collected 24h after infection and the production of IL-6 and TNF-α was measured by ELISA. Data show means ± SEM (**P < 0.005; ***P < 0.001). (E) RAW/Neo and RAW/AhR cells were transiently transfected with κB-luciferase reporter plasmid. Six hours after transfection, cells were infected with LM for a further 12h. The luciferase assay and quantitation were performed as described in Methods.

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Induction of AIM by AhR is critical for the inhibition of macrophage cell death in LM infection

To demonstrate the biological basis by which AhR protects against macrophage cell death induced by LM infection, we investigated the potential targets for AhR that are known to play important roles in antiapoptotic function. It has previously been demonstrated that LXR-induced AIM expression is important for macrophage survival [8].

To determine if AhR can control the expression of AIM during LM infection, we examined its expression in WT and AhR-deficient macrophages or RAW/Neo and RAW/AhR cells infected with LM. We found that AIM is robustly induced in AhR-expressing cells (Fig. 3A) and that the administration of AIM reduces LM-induced cell death in AhR KO macrophages (Fig. 3B). Similarly, AIM reduced LM-induced cell death in RAW/Neo cells (Fig. 3C). B-cell lymphoma 2 (Bcl2) is known to be an antiapoptotic protein [15].

Therefore, we compared its expression level between WT and AhR KO macrophages after LM infection. In contrast to AIM expression, AhR had no effect on the expression of Bcl2

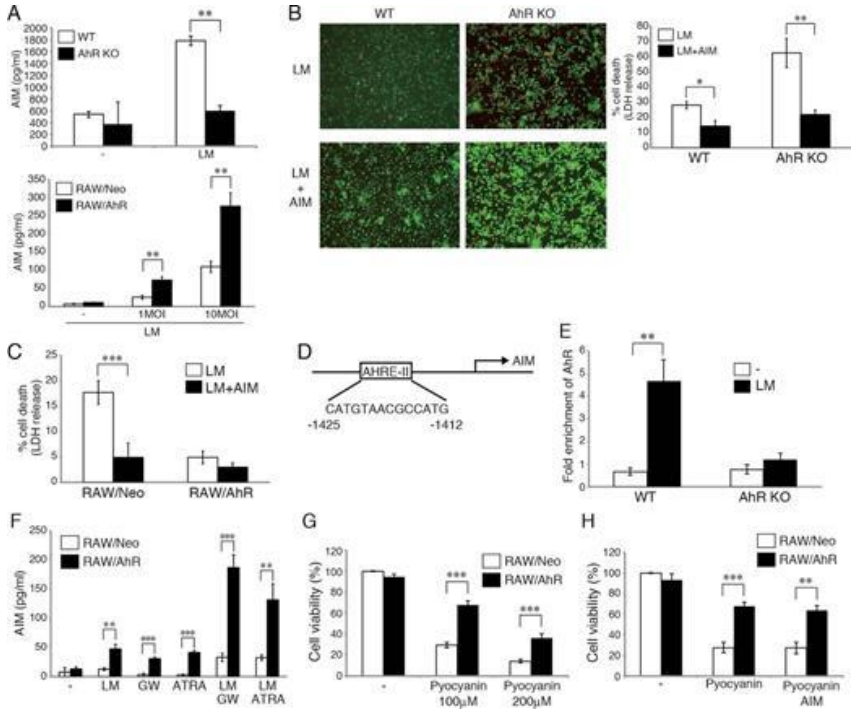

Figure 3.

AhR is required for the induction of AIM to prevent macrophage cell death induced by LM. (A) WT and AhR-deficient macrophages or RAW/Neo and RAW/AhR cells were infected with LM at an MOI of 1 and 10 for 24h. Supernatant was collected and AIM production was measured by ELISA. Data show means ± SEM (**$P < 0.005$). (B) WT and AhR-deficient macrophages were infected with LM at an MOI of 10 (Cell Imaging) or 20 (LDH release) in the presence or absence of AIM. At 24-h post-infection, cells were stained with a LIVE/DEAD Cell Imaging kit and live (green) and dead (red) cells were discriminated. Supernatant was collected for measurement of cell death by quantifying LDH release. Data show means ± SEM (*$P < 0.05$; **$P < 0.005$). (C) RAW/Neo and RAW/AhR cells were infected with LM at an MOI of 1 in the presence or absence of AIM for 24h.

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Discussion

here is growing interest in manipulating the AHR to modulate the function of immune system to alleviate the progression of immune-mediated diseases and treat cancer. However, it has long been known that some AHR ligands, such TCDD, are profoundly immunosuppressive. This raises concern that pursuing the AHR as a novel therapeutic target carries a risk of unintended adverse consequences, such as poorer ability to fight infection [18-22].

Also, although *in vitro* systems provide a means to screen activity and compare AHR ligands' effects at a cellular level, few studies have directly compared different AHR ligands on the same *in vivo* immune response. This makes it difficult to predict how AHR binding compounds will affect *in vivo* host responses to infection.

Moreover, when AHR ligands have been used *in vivo*, several reports describe a mixture of divergent and similar immunomodulatory effects, and we expand this knowledge base [23-27]. We show that *in vivo* treatment with each of these compounds affected aspects of the adaptive immune response to IAV infection. Yet, differences in ligand metabolism and binding affinity influence the impact on specific lymphocyte subtypes and on aspects of the adaptive response to infection.

This further supports that differences in the receptor, the 'strength' or duration of the signal, and events proximal to ligand-AHR interactions collectively influence the consequences of AHR activation on the immune response. This comparison provides important new information to consider as the AHR is explored as a potential therapeutic target and also for better understanding public health concerns about AHR-binding pollutants [28-30].

Previous work has shown that AhR KO mice are hyperresponsive to LPS and that AhR regulates innate immune responses [31]. In this study, we demonstrate that AhR KO mice are highly susceptible to LM infection, although AhR KO macrophages produced increased levels of pro-inflammatory cytokines, including IL-6 and TNF-α, during LM infection. On the other hand, a study showed that there is no difference in pro-inflammatory cytokine production between AhR KO and AhR heterozygous mice during LM infection [32]. However, they did not compare the levels of cytokines between AhR KO mice and littermate WT mice, which may have caused the discrepancy between our and their results. AhR negatively regulates LPS-induced pro-inflammatory cytokine production by interacting with NF-κB and inhibiting its activation [33].

In addition, the induction of many pro-inflammatory cytokines is suppressed by AhR activation in *Streptococcus pneumonia*-infected mice [34]. These observations are supportive of our data presented here. Along with TLR signaling, NOD-like receptors (NLRs) such as NOD1 and NOD2 contribute to host defense against microbial pathogens [11]. As reported herein, AhR can regulate both TLR and NLR signaling in macrophages infected with LM. Thus, although our results reveal AhR as a negative regulator of inflammatory signaling to protect the host from

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LM infection, AhR KO mice are more susceptible to listeriosis. These results suggest that AhR may have a unique function in protecting against LM infection [12].

One of the striking findings of this study is that AhR protects against macrophage cell death induced by LM infection [35]. To our knowledge, it has not been previously recognized that AhR is critical for host cell survival during bacterial infection. We found that AhR deficiency accelerates macrophage cell death dependent on the activation of caspase-3.

Interestingly, the number of peritoneal macrophages from AhR KO mice was less than the number from WT mice after LM infection, indicating that AhR is efficient for *in vivo* host macrophage survival. It is important to control the host cell death properly in LM infection. Macrophage cell death is an important mechanism for the down-regulation of inflammatory responses to prevent sepsis, whereas it has been reported that decreased macrophage apoptosis shows more resistance to LM infection [36, 37]. In this study, it has been demonstrated that AhR enhances the anti-microbial activity through inhibiting macrophage cell death.

Conclusion

This study highlights that AhR is a critical factor for the confinement and clearance of LM *in vitro* and *in vivo* by protecting against macrophage cell death and promoting ROS production. Additionally, our results suggest that appropriate ligand-activated AhR may bring about the optimal treatment for listeriosis. Although the mechanism by which AhR ligands mediate the resistance to LM infection requires further investigation, an important goal of this study has been to define the relationship between AhR ligands as environmental factors and the severe pathology in bacterial infection.

Competing interests

The authors declare that they have no competing interests.

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