VIRAL IMMUNOLOGY
Volume 32, Number 4, 2019

Pp. 161–169
DOI: 10.1089/vim.2019.0016

Original Articles

Targeting Peroxisome Proliferator-Activated Receptor-Gamma Decreases Host Mortality After Influenza Infection in Obese Mice

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Abstract

Obesity is an independent risk factor for severe influenza infection. However, the underlying cellular and molecular mechanisms are still incompletely understood. In this study, we have utilized a murine influenza infection model in genetic-induced obese (db/db) mice to explore the mechanisms by which obesity increases host susceptibility to influenza infection. We find that db/db mice have enhanced viral replication, exaggerated inflammatory responses, and dysregulated lung repair process after influenza infection, and consequently increased host mortality. Furthermore, we demonstrate that the transcription factor peroxisome proliferator-activated receptor-gamma (PPAR-γ), an important inflammation regulator, was downregulated in the lung macrophages of db/db mice after influenza infection. Strikingly, the treatment of 15-deoxy-Δ12, 14-prostaglandin J2 (15d-PGJ2), a PPAR-γ agonist, largely rescued the survival of db/db mice after influenza infection. Interestingly, macrophage PPAR-γ-deficient mice exhibited enhanced mortality after influenza infection and 15d-PGJ2 fails to rescue host mortality in macrophage PPAR-γ-deficient mice, suggesting that PPAR-γ expression in macrophages is critical for the action of 15d-PGJ2. These data indicate that obesity attenuates lung antiviral immunity and hampers host recovery through the modulation of macrophage PPAR-γ expression. Furthermore, modalities targeting macrophage PPAR-γ expression and/or function may serve as promising therapeutics to treat severe influenza infection in obese patients.

Keywords: PPAR-γ, obesity, macrophage

Introduction

Although majority of patients experience mild symptoms, influenza virus infection kills ~500,000 people globally and up to 50,000 people in the United States each year (61). High-risk populations such as young infants, aged individuals, pregnant women, and asthmatics are often more susceptible to influenza virus infection. In the 2009 H1N1 influenza pandemic, obese individuals were found to have higher incidence, increased hospitalization, more severe symptoms, and higher mortality compared with the general population (26,34,37,59,68). It is now recognized that obesity is an important independent risk factor for severe influenza infection. Several previous studies have explored the potential mechanisms by which obesity increases host susceptibility to influenza virus infection (12,25,44,45). For example, the proinflammatory milieu caused by aberrant accumulation of fat leads to the development of exaggerated inflammatory responses after influenza infection (58). Obese hosts also exhibited decreased titer of influenza-specific antibody and diminished function of antiviral CD8 T cells, resulting in delayed viral clearance and inflammation resolution (12,27). Furthermore, overweight reduces lung functional residual capacity as adipose tissue accumulated around chest and abdomen decreases lung compliance, resulting in exacerbation of flu infection (50). In addition, obese hosts also exhibit defective lung wound healing responses, thereby impairing lung damage repair after influenza infection (42). Although these studies have provided insights into the interplay between obesity and influenza infection, the underlying molecular mechanisms by which obese hosts are susceptible to severe influenza infection are still incompletely understood.

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Given the increasing prevalence of obesity worldwide (62), it is critical to understand the underneath mechanism for the purpose of influenza prevention and therapy.

Emerging evidence has suggested that lung macrophages play an important role in modulating antiviral responses and pulmonary inflammation after influenza infection. Obesity is associated with the recruitment of large numbers of inflammatory macrophages to the adipose tissue (38,60). Furthermore, obesity alters adipose tissue macrophage phenotypes, which drives persistent chronic inflammation in adipose tissues and facilitates insulin resistance (18). However, the effect of obesity on lung macrophage phenotype and function is unknown. The main macrophage population in the respiratory tract is alveolar macrophages (AMs) that play important roles in lung homeostasis and pulmonary antimicrobial defense (11,23,29,32). A number of factors, including peroxisome proliferator-activated receptor-gamma (PPAR-γ), were recently shown to be important in AM development and function (5,31,33,35,49).

PPAR-γ is a nuclear transcription factor, which forms complex with RXR (retinoid X receptor) for binding to PPAR-responsive regulatory elements in genome to promote gene transcription (1). In macrophages, PPAR-γ acts to restrict excessive production of inflammatory factors by antagonizing NF-κB function (30,46). Furthermore, PPAR-γ has been shown to be vital for the alternative polarization of macrophages (M2 MΦ) (6,16,17,43). The deficiency of PPAR-γ in AM caused severe defects in the maturation of AM compartment, suggesting that PPAR-γ is essential for AM development (35,52). Absence of PPAR-γ in lung macrophages causes enhanced Th1-biased inflammation and defective resolution of inflammation (15). Notably, prophylactic or therapeutic treatment of mice with natural or synthetic ligands that activate PPAR-γ leads to decreased pulmonary inflammation and host diseases during influenza virus infection (2,7,10,13,41), although the cellular mechanisms by which PPAR-γ agonists promote host protection against influenza infection have not been defined.

In this report, we show that genetic-induced obese db/db mice had enhanced host mortality after influenza infection. db/db mice exhibited enhanced viral replication, increased pulmonary inflammation, and decreased tissue recovery. Furthermore, we demonstrate that macrophage PPAR-γ is downregulated in db/db mice after influenza infection. PPAR-γ agonist 15d-PGJ2 treatment reversed host mortality after influenza infection. Our data suggest that the downregulation of PPAR-γ expression and/or function may underlie the enhanced host susceptibility to influenza virus infection in obese hosts.

Materials and Methods

Mouse and infection

WT C57/BL6,db/+ heterozygous [B6.BKS(D)-*Lepr^{db}*/J, JAX: 000697], Lyz2-cre, *Pparg$^{fl/fl}$* mice were purchased from the Jackson Laboratory and bred in house. db/db mice were obtained by crossing db/+ mice. *Pparg$^{\Delta Lyz2}$* mice were generated by crossing *Pparg$^{fl/fl}$* mice with Lyz2-cre mice. All control mice are age- and gender-matched WT mice from the same litter. All mice housed in a specific pathogen-free environment. For influenza virus infection, influenza A/PR8/34 strain ($\sim$200 pfu/mouse) was diluted in fetal bovine serum-free Dulbecco's modified Eagle's medium media (Corning) on ice and inoculated in anesthetized mice through intranasal route as described before (55). All mouse procedures were approved by the Institutional Animal Care and Use Committee (IACUC) of the Indiana University (No. 10006) or the Mayo Clinic (No. A00002027).

Lung single cell preparation

Mice were euthanized through overdose ketamine followed by cervical dislocation. Lungs were perfused through the right ventricle of the heart with 10 mL phosphate-buffered saline (PBS) to remove blood mononuclear cells from the vasculature [modified from a previous report (21)]. Subsequently, lung tissue was minced into small pieces and enzymatically digested with type II collagenase (37°C for 30 min; Worthington), followed by passing through a steel screen. RBCs in the cell suspensions were lysed using ammonium chloride. Cells were counted using a hemocytometer after exclusion of dead cells using Trypan blue dye and suspended at appropriate concentrations for each experiment.

Bronchoalveolar lavage cytokine assay

Bronchoalveolar lavage (BAL) was obtained by flushing the airway multiple times with a single use of 600 μL sterile PBS for cytokine analysis as previously described (67). Supernatants collected from first BAL flush were subjected for cytokine measurement by Multiplex (Millipore) according to the user manual. The result was read with Luminex instrument and analyzed with Milliplex software (Millipore).

Quantitative Reverse Transcriptase PCR

mRNA from the homogenates of the lungs as indicated in the text was isolated with Total RNA purification kit (Sigma) and treated with DNase I (Invitrogen) as previously described (19). Random primers (Invitrogen) and MMLV reverse transcriptase (Invitrogen) were used to synthesize first-strand cDNAs from equivalent amounts of RNA from each sample. Quantitative Reverse Transcriptase PCR (qPCR) was performed with Fast SYBR Green PCR Master Mix (Applied Biosystems). qPCR was conducted in duplicates in QuantStudio3 (Applied Bioscience). Data were generated with the comparative threshold cycle (Delta CT) method by normalizing to hypoxanthine phosphoribosyl transferase. Sequences of primers used in the studies will be provided upon request.

Mouse wound healing RT^2 profiler PCR array

Total RNA from lung tissue was extracted as described earlier. Equal amount of total RNA was used for the synthesis of first-strand cDNA with kit from Qiagen. First-strand cDNA was mixed with 2xFast SYBR Green Master Mix (Applied Bioscience) and water in a formula directed in the manual. Twenty-five microliters of the mixture was added into each well of the 96-well plate provided by the manufacturer. The wells in the plate include different primers in each well to detect 84 target genes, housekeeping genes, and negative and positive control genes. qPCR was conducted in QuantStudio3 (Applied Bioscience). Obtained raw data were analyzed in software provided by Qiagen

(accessible online on the website of Qiagen). Following the instruction step by step, upload Excel file, designating control group, select housekeeping gene to normalize result, and calculate the relative expression quantity.

Western blot analysis

Fluorescence Acivated Cells Sorting (FACS)-sorted AMs were lysed in lysis buffer (62.5 mM Tris-HCL [pH 6.8], 2% SDS (sodium dodecyl sulfate) and 10% glycerol) with a protease inhibitor cocktail (Roche). The lysates were then separated by SDS-PAGE (SDS–polyacrylamide gel electrophoresis) and transferred to Immuno-Blot Nitrocellulose Membrane (Bio-Rad). The membranes were blocked with 5% nonfat milk in 20 mM Tris (pH 7.5), 0.5 M NaCl, and 0.05% Tween 20 (TBST) for 1 h at room temperature, followed by incubation with primary Ab against PPAR-γ (1:1,000; Cell Signaling Technology) or β-actin (1:5,000; Santa Cruz Biotechnology) overnight at 4°C. After washing with TBST buffer, membranes were incubated with goat anti-rabbit or anti-mouse secondary Ab (Promega). Peroxidase activity was detected with enhanced chemiluminescence.

Plaque assay

Influenza plaque assays were performed as described before (22,66). In brief, MDCK cells were grown in six-well plates and incubated with series dilution of bronchoalveolar lavage fluid (BALF) for 1 h. The plates were then overlaid with low melting temperature agarose (0.6%) in minimum essential medium (MEM) with bovine serum albumin and trypsin and cultured for 3 days in 37°C incubator. Plates were then fixed with formaldehyde and virus plaques were visualized with the staining of neutral red.

FACS analysis

Fluorescence-conjugated FACS Abs were purchased from Biolegend, BD Biosciences or eBioscience. We defined cell populations based on following cell surface markers: AM ($CD11c^+$ Siglec F^+ $CD11b^{low}$), NP_{366} $tetramer^+$ cells ($CD8^+$ $H2d^b$ NP_{366}-tet^+). Samples were collected on FACS Attune or FACS Attune NXT flow cytometer (Life Technologies), and analyzed using Flow Jo software (Tree Star).

15d-PGJ2 treatment

15d-PGJ2 was purchased from Sigma (Cat. No. D8440) and dissolved in methyl acetate (1 mg/mL). The vehicle was replaced with PBS before administration through evaporation by nitrogen gas. Owing to the short half-life time of 15d-PGJ2 in PBS, the vehicle replacement was done separately one by one. 15d-PGJ2 was given by intra peritoneal (IP) injection at 250 ng/g body weight daily from 1 to 12 d.p.i. (days postinfection).

Statistical analysis

Data are mean ± standard error of the mean of values from individual mice (*in vivo* experiments). Unpaired two-tailed Student's *t*-test (two group comparison), multiple *t*-tests (weight loss), or log-rank test (survival study) were used to determine statistical significance by GraphPad Prism software. We consider $p < 0.05$ as significant.

Results

Enhanced host mortality and impaired viral clearance in obese mice after influenza infection.

To explore the underneath mechanism of susceptibility of obese individuals to influenza infection, a murine influenza infection model was employed, in which we infected the genetic-induced obese db/db mice with influenza A/PR8/34. db/db mice harbor point mutations in the leptin receptor, which resulted in obesity syndromes in mice (Fig. 1A) (9). Consistent with reported observations (40,42), db/db mice exhibited milder body weight loss compared with that of control mice after influenza infection (Fig. 1A). However, db/db mice showed significantly enhanced host mortality after infection (Fig. 1B). The increased host mortality in db/db mice was correlated with the failure of viral clearance in db/db mice, as we observed significant higher influenza titers in the lungs of db/db mice at 10 d.p.i. (Fig. 1C). Since antiviral T cell responses are important in clearing influenza virus from the lungs (4,54), we examined CD4 and CD8 T cell responses in WT and db/db mice at day 7 and 10 p.i. Strikingly, we found that both the total numbers of CD4, CD8 T cells and the influenza antigen-specific CD8 T cells [as enumerated through the staining of $H2d^b$ $NP_{366–374}$ tetramer (NP)] were diminished in db/db mice than those in control lean mice (Fig. 1D, E). Taken together, obesity leads to decreased host antiviral immune response, which resulted in enhanced viral replication and increased host mortality.

Enhanced lung inflammation and impaired wound healing in obese mice

In addition to virus-induced lung damage, exuberant inflammatory responses also contribute to lung damage and disease development after influenza infection. To this end, we examined whether obese mice had enhanced pulmonary inflammation after influenza infection. The profiles of cytokines and chemokines in BALF of WT or db/db mice were determined at 7 or 10 days after influenza infection. We found that db/db mice showed widespread increased inflammatory cytokine levels in BALF (Fig. 2A, B), indicating enhanced pulmonary inflammation in db/db mice after influenza infection.

To return normal homeostasis, damaged lung tissues need to be repaired after viral control. A previous study has suggested that obese hosts have diminished lung repair (42), although the molecular mechanisms underlying the phenomena were not determined. To this end, we used Qiagen wound healing PCR array method to examine lung repair gene expression in WT or db/db mice at day 10 p.i. We found that multiple wound healing genes were downregulated in the lungs of db/db mice at 10 d.p.i. compared with control lean mice (Fig. 2C). Those downregulated genes include epithelial and endothelial growth factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and lung remodeling factors such as collagens and matrix metalloproteinases (Fig. 2C, D). Together, these data suggest that db/db mice had dysregulated damage repair function after influenza infection. The re-expression of lung type II alveolar epithelial cell (AEC II) genes are commonly used as an indicator of lung injury repair (14). We, therefore, determined AEC II gene expression and found that lungs from db/db mice showed diminished expression of multiple

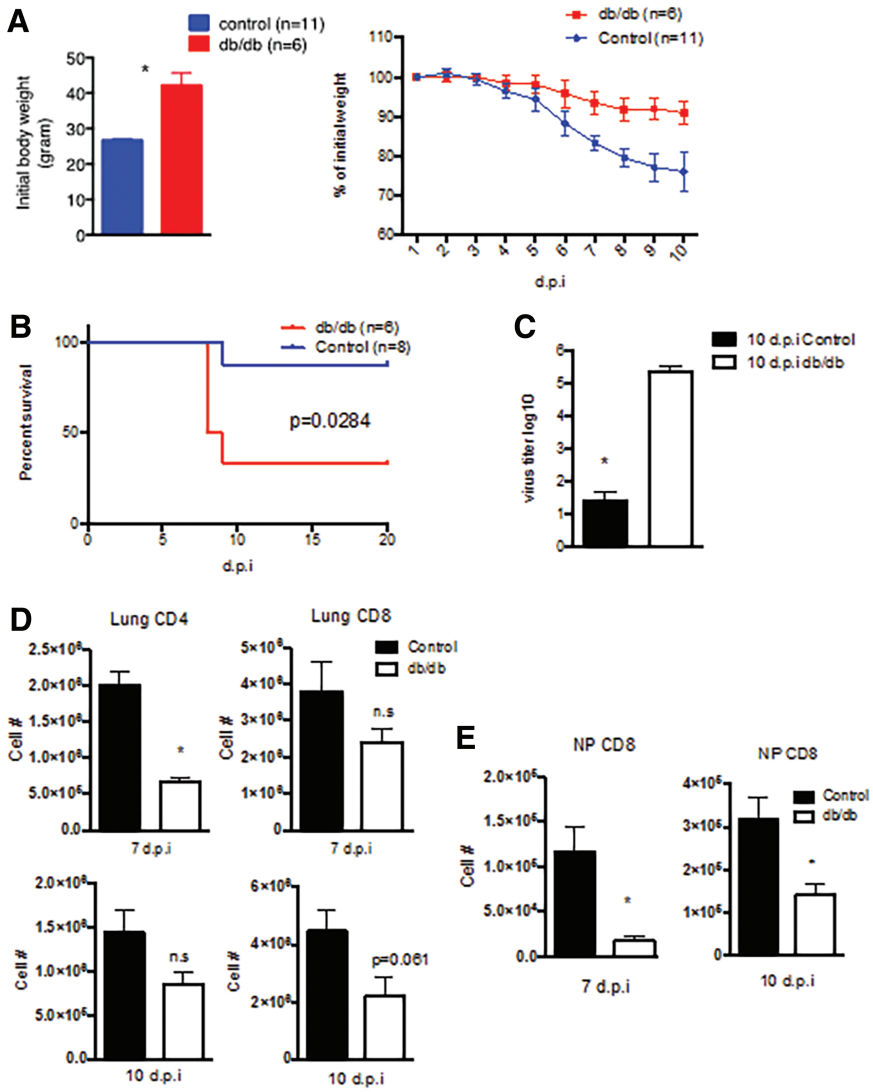

FIG. 1. Enhanced host mortality and impaired viral clearance in db/db mice after influenza infection. Littermate WT control or db/db mice were infected with influenza PR8. **(A)** Host initial weight (*left panel*) and morbidity (% initial weight) (*right panel*) after infection were monitored daily. **(B)** Host mortality (% survival) was monitored. **(C)** Airway influenza titers (pfu/mL) were determined at day 10 p.i. **(D)** Numbers of total CD4, CD8 T cells in the lungs at day 7 or 10 p.i. **(E)** Numbers of influenza-specific CD8 T cells ($H2D^b$ $NP_{366–374}$ $tetramer^+$, NP CD8) in the lungs at day 7 or 10 p.i. Data are representative of two experiments. Survival data were analyzed by log-rank (Mantel–Cox) test and all other data were analyzed by two-tailed Student's *t*-test. *Represents significant differences ($p < 0.05$). Color images are available online.

AEC II genes than those of WT mice (Fig. 2E), confirming the impaired damage repair in db/db lung.

Diminished PPAR-γ expressions in lung macrophages of db/db mice before and after influenza infection

Multiple immune cells are involved in orchestrating host initial inflammatory reaction after influenza virus infection. Among these cells, lung macrophages exhibit unique roles in regulating inflammation, immunity, and repair after influenza infection (64). We have recently showed that conditional knockout of PPAR-γ in macrophages led to enhanced inflammation and diminished damage repair after influenza infection (20). Therefore, we wanted to determine whether obesity could affect the expression of PPAR-γ in lung macrophages after influenza infection. Sorted lung macrophages ($CD45^+CD64^+$/$MERTK^+$) from naïve mice and influenza-infected mice were lysed and the amount of PPAR-γ protein in macrophages was directly measured by western blot. We found that the protein levels of PPAR-γ in lung macrophages of db/db mice were modestly lower than those of control lean mice before infection (day 0) (Fig. 3). Furthermore, PPAR-γ levels in lung macrophages were markedly decreased in db/db mice compared with those in control lean mice after influenza infection (5 and 9 d.p.i.). Together, these data indicate that obesity suppresses the expression of PPAR-γ in lung macrophages after influenza infection.

15d-PGJ2 promotes macrophage PPAR-γ-dependent host recovery

We have shown previously that macrophage-specific PPAR-γ deficiency caused enhanced host morbidity and mortality after influenza infection (20). Interestingly, a PPAR-

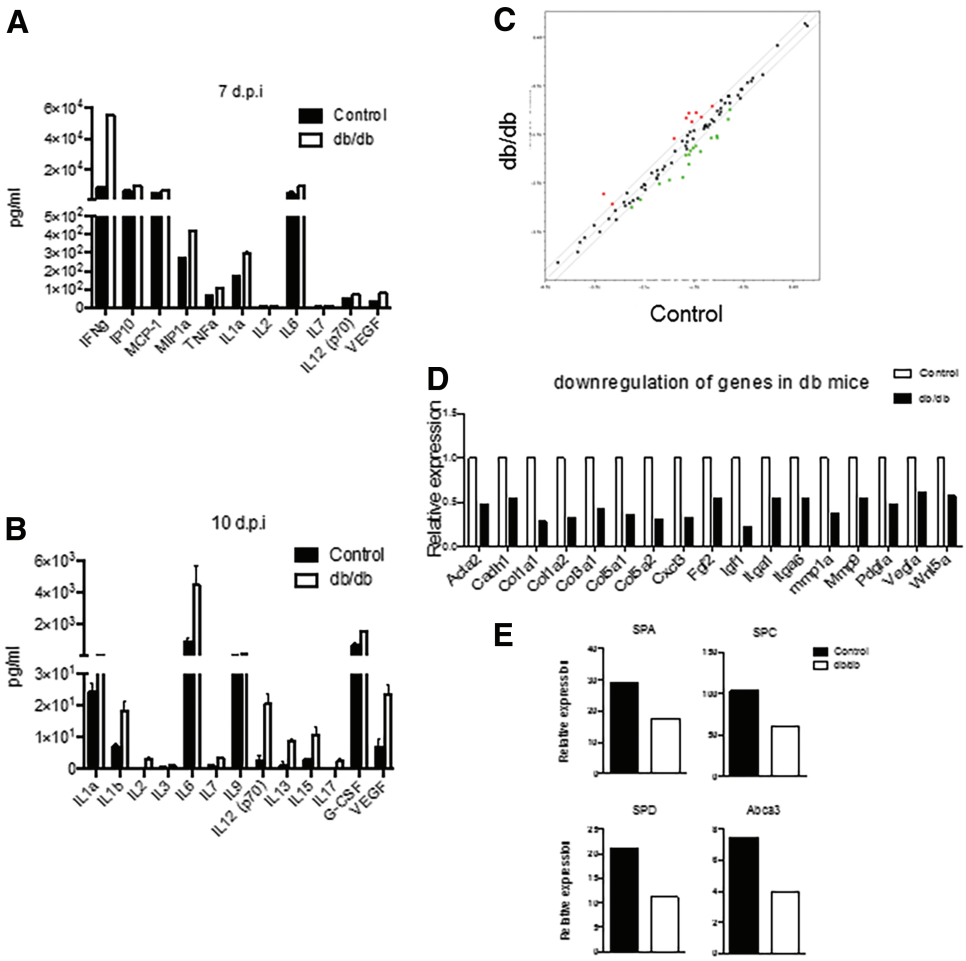

FIG. 2. Enhanced inflammation and impaired wound healing in db/db mice. Littermate WT control or db/db mice were infected with influenza PR8. **(A)** BAL cytokines levels in control or db/db mice at day 7 p.i. were determined by multiplex cytokine analysis. **(B)** BAL cytokines levels in control or db/db mice at day 10 p.i. were determined by multiplex cytokine analysis. **(C)** Comparison of the expression of 84 wound healing genes in the lungs at day 10 p.i. by RT^2 Profiler PCR array. *Dotted line,* fold cutoff of gene expression (1.5-fold). *Red dots*, genes upregulated in the lungs of db/db mice. *Green dots*, genes downregulated in the lungs of db/db mice. **(D)** Repair-associated genes in the PCR array **(C)** that were downregulated in the lungs of db/db mice. **(E)** qRT-PCR analysis of type II AEC genes expression at 10 d.p.i. (pooled cDNA samples from two to three mice per group). Data are representative of at least two experiments. Data were analyzed by two-tailed Student's *t*-test. All graphs in **(A) (B)** represent significant differences ($p < 0.05$). AEC, alveolar epithelial cell; BAL, bronchoalveolar lavage; d.p.i. days postinfection; qRT-PCR, quantitative Real time PCR. Color images are available online.

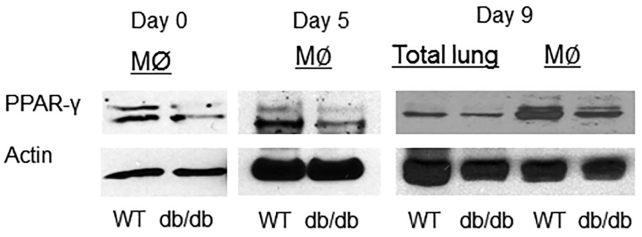

FIG. 3. Diminished PPAR-γ expression in lung macrophages of db/db mice. Littermate WT control or db/db mice were infected with influenza PR8. Lung macrophages ($CD45^+/MerTk^+/CD64^+/Ly6G^-$) were sorted before infection (day 0) or at indicated days after infection. PPAR-γ and actin levels in the sorted macrophages were determined by western blot analysis. Data are representative of at least two experiments. PPAR-γ, peroxisome proliferator-activated receptor-gamma.

γ agonist, 15d-PGJ2, could enhance host recovery in WT lean mice (7), although the underlying cellular mechanisms are not clear currently. We hypothesize that macrophage PPAR-γ expression is required for 15d-PGJ2 effects. To this end, we infected control or macrophage-specific PPAR-γ-deficient mice (Lyz2-cre $Pparg^{fl/fl}$ mice, $Pparg^{\Delta Lyz2}$) with influenza and then treated the mice with 15d-PGJ2. In control $Pparg^{fl/fl}$ mice, 15d-PGJ2 treatment exerted protective effects and ameliorated host morbidity (Fig. 4A). However, 15d-PGJ2 treatment failed to increase host recovery and did not rescue the enhanced host mortality in $Pparg^{\Delta Lyz2}$ mice (Fig. 4B), suggesting that the protective effects of 15d-PGJ2 against influenza infection require PPAR-γ expression in macrophages.

PPAR-γ agonist treatment decreases host mortality of db/db mice

The aforementioned data suggest that attenuated expression and/or activity of PPAR-γ may contribute to the

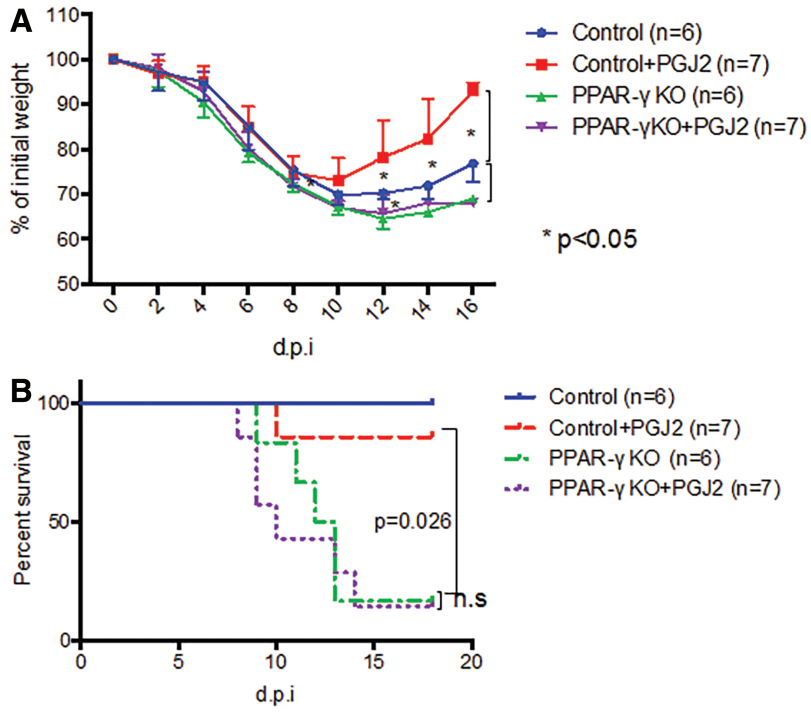

FIG. 4. Deletion of PPAR-γ in macrophages abolishes the effect of 15d-PGJ2. WT littermate control ($Pparg^{fl/fl}$) or $Pparg^{\Delta Lyz2}$ mice were infected with influenza PR8 and treated with vehicle or 15d-PGJ2. **(A)** Host morbidity (% initial weight) after infection was monitored daily. **(B)** Host mortality (% survival) was monitored. Data are pooled from two experiments. Survival data were analyzed by log-rank (Mantel–Cox) test and weight loss data were analyzed by multiple *t*-test. *Represents significant differences ($p < 0.05$). Color images are available online.

enhanced disease development after influenza infection in obese mice. We next sought to determine whether the stimulation of PPAR-γ activity could ameliorate host diseases after influenza infection in obese mice. To this end, we infected WT or db/db mice with influenza and then treated the mice with 15d-PGJ2. As reported (3,7), 15d-PGJ2 treatment enhanced host recovery in lean mice as 15d-PGJ2-treated mice exhibited earlier body weight regains (Fig. 5A). Strikingly, 15d-PGJ2 treatment promoted db/db mouse survival, rising from 11% to 55% survival rate (Fig. 5B). Together, data in Figures 4 and 5 indicate that enforced macrophage PPAR-γ activation may attenuate host disease development after influenza infection in obese hosts.

Discussion

Obesity is known to be an independent risk factor associated with various disorders such as cardiovascular diseases and type 2 diabetes. Recently, obesity was also identified as a risk factor for severe influenza infection (8,39,65). Consistent with the clinical findings, obese mice exhibit increased mortality, enhanced lung inflammatory responses, and impaired tissue recovery when compared with control lean mice (53). Our results are consistent with those reported findings. Furthermore, we have demonstrated that obese mice have altered antiviral adaptive immune responses, impaired viral clearance, decreased wound healing gene expression, and defective regeneration of lung AEC II cells. These altered host responses to influenza infection likely all contribute to the enhanced host mortality after influenza infection in obese mice.

Macrophages are important regulators of host responses against influenza infection (51). Absence of the major lung resident macrophage population, that is, AM, results in severe lung damage and enhanced host mortality after influenza infection (5,31,49,51). Conversely, diminished recruitment of inflammatory monocytes and macrophages leads to decreased host inflammation and disease development (36). Thus, different macrophage populations may exhibit distinct function to influenza infection. Currently, the transcriptional regulation of lung macrophage function during influenza virus infection is poorly understood. We recently have identified that PPAR-γ deficiency in macrophages led to enhanced pulmonary inflammation and diminished lung repair at acute phase (20). In this report, we have found that obesity decreased the anti-inflammatory transcription factor, PPAR-γ, expression in lung macrophages before and after influenza infection. Consistent with the observation, obese mice exhibited enhanced pulmonary inflammation and impaired tissue repair, which mimic the phenotypes observed in the macrophage-specific PPAR-γ-deficient mice. Together these data suggest that diminished PPAR-γ expression and/or activity in macrophages could underlie the enhanced susceptibility to severe influenza infection in obese hosts.

In support of this idea, 15d-PGJ2 treatment improved the poor outcome of infected obese mice. Furthermore, the specific deletion of PPAR-γ in macrophages abolished the effects of 15d-PGJ2 treatment. Thus, our data have provided a viable mechanism by which obesity increases host susceptibility to influenza infection. Nevertheless, obesity is likely to pose significant effects on multiple cell types and

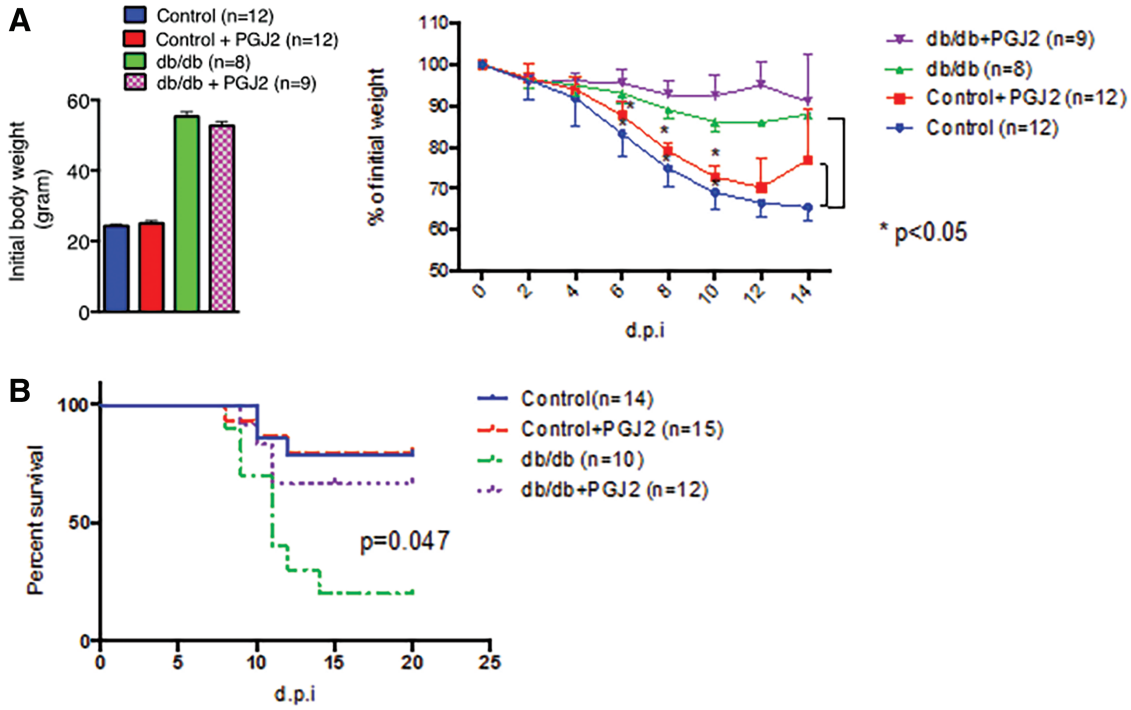

FIG. 5. PPAR-γ agonist diminishes host mortality in db/db mice after influenza infection. Littermate WT control or db/db mice were infected with influenza PR8 and treated with vehicle or 15d-PGJ2. **(A)** Host initial weight (*left panel*) and morbidity (% initial weight) (*right panel*) after infection were monitored daily. **(B)** Host mortality (% survival) was monitored. Data are pooled from three experiments. Survival data were analyzed by log-rank (Mantel–Cox) test and weight loss data were analyzed by multiple *t*-test. *Represents significant differences ($p < 0.05$). Color images are available online.

molecular pathways to increase host susceptibility to severe influenza infection. For instance, reduced antiviral type I interferon production and/or signaling due to the increased suppressor of cytokine signaling (SOCS) activities may also contribute to the severe influenza infection in obese mice (47). Of note, we have not examined the mechanisms of action by which 15d-GPJ2 treatment inhibits host mortality after influenza infection in obese mice. A previous report has suggested that 15d-PGJ2 treatment can simultaneously promote viral control and suppress host inflammation (7). Thus, it is possible that 15d-PGJ2 could restore viral control and inhibit inflammatory responses in db/db mice. Furthermore, 15d-PGJ2 may also promote lung repair process in db/db mice since PPAR-γ expression in macrophages is important in tissue repair after influenza infection (20). Future studies are needed to explore these possibilities.

Delayed or impaired wound healing responses are a distinguishing feature of obesity subjects (42). Obesity can lead to impaired cutaneous repair commonly found in surgery patients (48). We found that obese mice exhibited a general trend of downregulation of wound repair genes at day 10 postinfection, when normal lean mice started to recover their weight and repair the damaged lung tissues (42,56,57). These data indicate that obesity also dysregulates the healing responses to lung wound in addition to the cutaneous wound. Of note, macrophages are critical regulators of wound repair responses. They can phagocytose cells debris, release healing cytokines and chemokines, and recruit various other helper cells to create optimistic environment for tissue remodeling (63,64). We speculate that obesity may directly interfere with macrophage-mediated wound healing responses through the downregulation of PPAR-γ. PPAR-γ expression in macrophages is important for their expression of multiple epithelial and endothelial growth factors (20,24,28). However, it is also possible that increased viral replication and/or increased pulmonary inflammation may contribute to the decreased wound healing responses observed in obese mice. Future studies are warranted to explore these possibilities.

In summary, we have identified that obesity dysregulates host antiviral, inflammatory, and reparative responses, potentially through the inhibition of macrophage function through PPAR-γ downregulation. Furthermore, our data suggest that drugs that can stimulate macrophage PPAR-γ function may serve as promising therapeutics to treat severe influenza infection in obese patients.

Acknowledgments

We thank NIH tetramer facility for providing influenza-specific tetramers and Mayo flow cytometry core for help of cell sorting. This study was supported by the U.S. National Institutes of Health grants (RO1 HL126647, AG047156, and AI112844) and Kogod Aging Center High Risk Pilot Grant to J.S.

Author Disclosure Statement

No competing financial interests exist.

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