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# Salvianolic acid B ameliorates liver injury in a murine aGvHD model by decreasing inflammatory responses via upregulation of HO-1

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ABSTRACT

Acute graft-versus-host disease (aGvHD) remains lethal, even after allogeneic hematopoietic stem cell transplantation. Inflammatory responses play an important role in aGvHD. Salvianolic acid B (Sal B) has been widely reported to have a major effect on the anti-inflammatory response, but these effects in an aGvHD model have never been reported. B6 donor splenocytes were transplanted into unirradiated BDF1 recipients and liver and serum were collected on day 14 after transplantation with or without Sal B administration. We measured the expression of pro-inflammatory cytokines and chemokines and other manifestations in aGvHD mice after Sal B treatment. Sal B ameliorated liver injury in aGvHD and promoted survival in mice. Sal B treatment resulted in decreased expression of pro-inflammatory cytokines and chemokines whose expressions in liver are normally elevated by aGvHD. Furthermore, Sal B treatment also enhanced PGC-1α expression in liver tissue and HO-1 expression in nonparenchymal cells. In addition, HO-1 inhibitor abrogated the improvement of survival rate of mice with aGvHD. These results indicated that the protective effect of Sal B relies on suppressing the inflammatory response phase in the aGvHD model, presumably by inducing HO-1. Taken together our data showed that Sal B ameliorates liver injury in aGvHD by decreasing inflammatory responses via upregulation of HO-1. It may provide a novel way to deal with this disease.

## 1. Introduction

Acute graft-versus-host disease (aGvHD) is still a major problem that hampers allogeneic hematopoietic stem cell transplantation treatment of hematologic malignancies and other blood diseases [1]. During the development of aGvHD, whose end-organ damage focuses on liver, skin, lungs, and gut, inflammatory responses play very important roles and result in tissue damage [2,3]. Several strategies are being pursued to treat aGvHD and current therapies include administration of extracellular mediators and receptors, regulation of intracellular signaling pathways, and regulation of translation and transcription [4]. A successful decreasing of inflammatory responses is one of the major strategies to deal with aGvHD.

Salvianolic acid B (Sal B) is a major water-soluble component extracted from *Salviae miltiorrhizae* and is a widely used herbal ingredient in China for various kinds of diseases. Several in vitro and in vivo experiments have reported that Sal B has not only antioxidant and antitumor effects, but also has anti-inflammatory effects through different pathways [5–14]. Here, in our experiment, we assessed whether administration of Sal B ameliorates liver injury and improves survival of aGvHD mice.

## 2. Materials and methods

### 2.1. Animals

All animals in this experiment were used in accordance with the recommendations in the Guide for the Care and Use of Laboratory

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Animals of the National Institutes of Health. The protocol was approved by the Committee on the Ethics of Animal Experiments of the National Center for Child Health and Development, Tokyo, Japan. Male C57BL/6(B6)(H-$2^b$) mice (8–12 weeks old) were purchased from SLC (Shizuoka, Japan) and male (C57BL/6 × DBA/2) F1(BDF1)(H-$2^{b/d}$) mice (8–12 weeks old) were purchased from CLEA Japan, Inc. (Tokyo, Japan). All the mice were kept under specific pathogen-free conditions.

### 2.2. aGvHD mouse model

aGvHD was induced by intravenous injection of $1 \times 10^8$ viable B6 donor splenocytes into unirradiated BDF1 recipients [15,16]. All the donor and recipient mice were age and sex matched. At the indicated time point, on day 14 [17,18], mice were sacrificed and serum and liver tissues were collected for measurement of liver enzymes (aspartate transaminase [AST] and alanine transaminase [ALT]) and RNA analysis.

### 2.3. Experimental protocol

The mice were divided into three study groups, as follows: (1) Naïve group: normal BDF1 host mice with PBS treatment (Naïve); (2) Control group: aGvHD model mice, treated with PBS (Control); (3) Sal B group: aGvHD model mice, intraperitoneal injection of Sal B (100 mg/kg) (Sal B). All the mice from the Control group and Sal B group were treated with PBS or Sal B, respectively, once daily from the day of injection with the B6 donor splenocytes until the indicated time point, on day 14. The Naïve group was treated with PBS for 14 days. Zinc protoporphyrin IX (ZnPPIX; Sigma-Aldrich, Saint Louis, MO), an HO-1 inhibitor, was administered simultaneously with Sal B. Sal B was purchased from Shanghai Standard Technology Co., Ltd. (Shanghai, China).

### 2.4. Histological analysis

Livers were dissected and fixed in 4% paraformaldehyde for 2 h, embedded in paraffin, and cut into 4-μm thick sections. The sections were stained with hematoxylin and eosin (H&E). The histological assessment was performed according to the scoring system as previously described with slight modification [19,20]. Scoring was performed in a blinded manner.

### 2.5. Liver enzyme measurement

Liver function was measured by AST and ALT levels. AST and ALT levels in mice serum were tested by chips from Fujifilm, Japan, following the manufacturer's protocol.

### 2.6. Isolation of nonparenchymal cells from liver

Nonparenchymal cells (NPCs) were isolated as previously described with slight modification [21,22]. Briefly, the liver was mashed and passed through a 70-μm nylon cell strainer on ice; then, after 8–10 min subsided, the supernatant was collected for washing 2 times with PBS. NPCs were purified by centrifugation at room temperature for 25 min over a 40%/70% discontinuous Percoll gradient (Sigma-Aldrich). The NPCs were suspended in Buffer RLT for quantitative real-time PCR analysis.

### 2.7. RNA preparation and quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) analysis

To measure target mRNA expression levels, total RNA was isolated from liver tissue and liver NPCs using ISOGEN (Nippon Gene, Tokyo, Japan) following the manufacturer's protocol [23,24]. In brief, RNAs were reverse transcripted to cDNAs by using the PrimeScript TR reagent kit (Takara Bio, Shiga, Japan). The target-specific primers and probes were designed as described previously [23,24] and synthesized by Biosearch Technologies, Inc. (Novato, CA). PCR was performed in a 25-μL reaction mixture containing 12.5 μL 2 × Premix Ex TaqTM (Takara Bio), 5 pmol of primer, and 6.5 μL of cDNA obtained as described above. Amplification was conducted on the Applied Biosystem PRISM7700 (ABI Japan, Co., Ltd., Tokyo, Japan). The PCR cycling conditions were as follows: 95 °C for 30 s, 40 cycles 95 °C for 5 s, and 60 °C for 30 s, 25 °C for 2 min. Quantification was determined by the standard curve and $2^{-\Delta\Delta}$Ct methods. 18S was used as an internal control to normalize all PCR products.

### 2.8. Statistical analysis

All data were analyzed by GraphPad Prism 7 (GraphPad Prism Software Inc., San Diego, CA) and presented as the mean ± SEM. The Student *t*-test, Mann-Whitney test, or one-way ANOVA were performed to determine significance differences among groups. The survival probability was analyzed by the Kaplan-Meier curve and the log rank test was performed to determine the effect. Significance was reported at $p < .05$.

## 3. Results

### 3.1. Sal B ameliorated liver injury in aGvHD

Liver injury in aGVHD mainly presented as endothelialitis, lymphocytic infiltration of the portal areas, pericholangitis, and bile duct destruction [1,25]. We measured lymphocytic infiltration by H&E stain to show how it presents among the Naïve, Control, and Sal B groups. As shown in Fig. 1A and B, Sal B protected the liver from aGvHD injury. In addition, our data showed that high AST and ALT levels in serum were consistent with lymphocytic infiltration in liver, whereas Sal B treatment showed significant decreases in the serum levels of AST and ALT (Fig. 1C and D). Furthermore, Sal B increased the survival probability in aGvHD, whereas this effect was diminished by ZnPPIX, an inhibitor of HO-1 (Fig. 1E).

### 3.2. Sal B suppresses inflammatory responses and M1-type macrophage markers in liver

In order to analyze how Sal B ameliorated liver injury, we assayed by qRT-PCR several kinds of pro-inflammatory cytokines in liver tissue, such as TNF-α, IL-6, IL-1β, and IFN-γ, which are the major contributors to the development of aGvHD and lead to end-organ damage [2,16,26]. As shown in Fig. 2, expression of TNF-α, IL-6, IL-1β, and IFN-γ was elevated in aGvHD, whereas Sal B treatment decreased expression of TNF-α, IL-6, IL-1β, and IFN-γ. Furthermore, Sal B showed decreases in M1-type macrophage markers, including CCL2, CCR2, and iNOS, in addition to TNF-α (Fig. 2). Our data demonstrated that Sal B suppressed the inflammatory response in aGvHD.

### 3.3. Sal B upregulated HO-1 expression in NPCs and PGC-1α in liver tissue

Previous reports showed that HO-1 has an anti-inflammatory effect [27–33] and has a protective effect in aGvHD disease [34–37], which is why we checked HO-1 expression in liver tissue. The HO-1 expression level was significantly increased in the aGvHD and Sal B group compared with Naïve, whereas HO-1 expression in the Sal B treatment group was comparable to Control in liver tissue (Fig. 2). We further measured the HO-1 expression in NPCs and found that the high expression of HO-1 in Sal B-treatment mice compared significantly with Control (Fig. 3). In addition, we checked PGC-1α expression, which had a protective effect from inflammation in liver tissue [38–40]. As shown in Fig. 2, PGC-1α had a significantly higher expression in Sal B-treatment mice in comparison with Control.

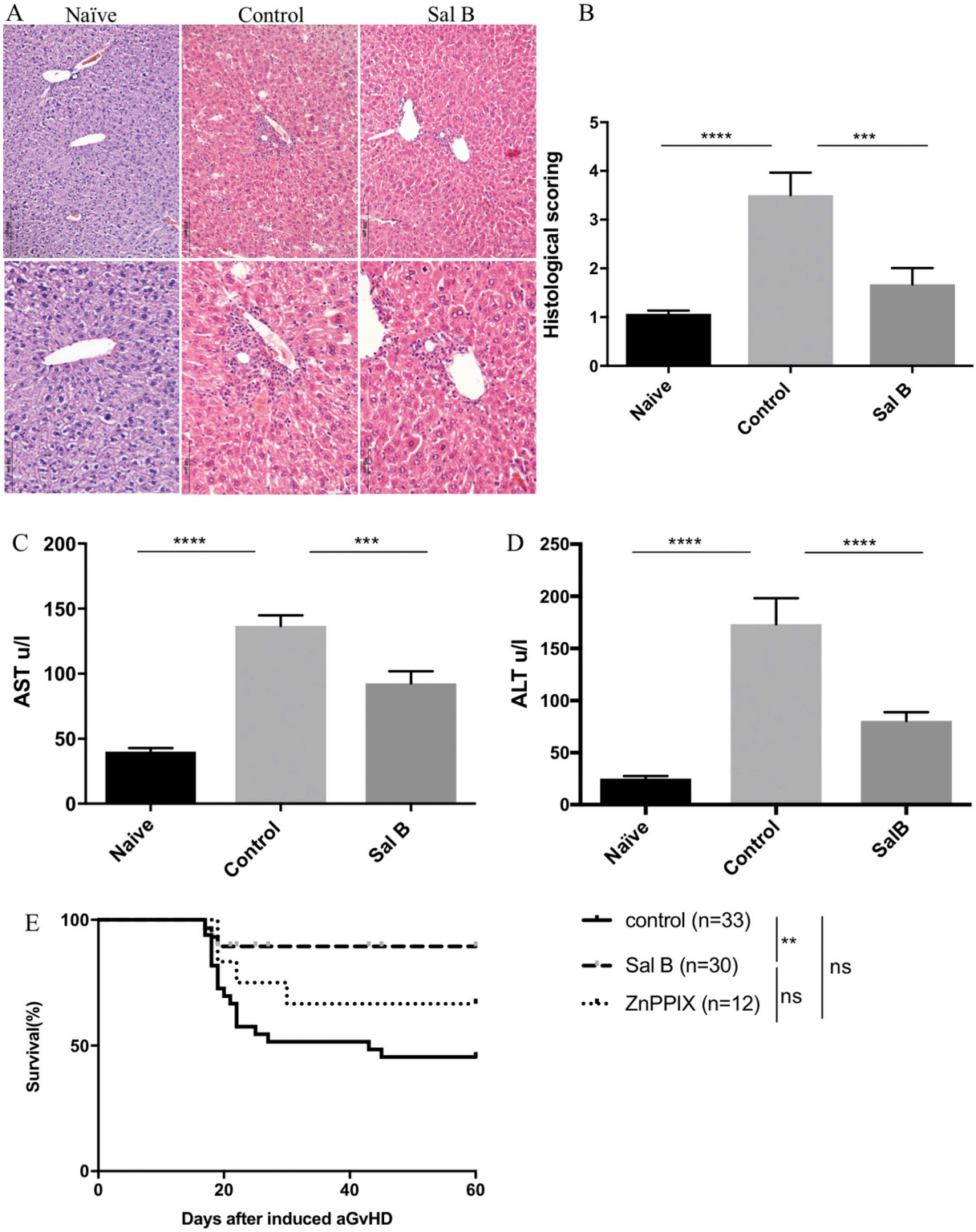


**Fig. 1.** *Sal B effect on liver and survival in aGvHD mice*. Liver tissue samples were collected on day 14. (A) Lymphocytic infiltration is shown by H&E stain. Magnification is indicated in each photomicrograph. (B) Histology scoring was performed as described in Materials and Methods. Serum samples were collected on day 14 and AST (C) and ALT (D) serum levels were measured. (E) Mice were treated with Sal B alone and Sal B together with ZnPPIX for 14 days, PBS-treated aGvHD mice served as controls. Animals were monitored for survival. Data were analyzed and presented as the mean ± SEM. $^{**}p < .01$, $^{***}p < .001$, $^{****}p < .0001$ as compared with the Control group.

## 4. Discussion

There were already many reports which showed that Sal B has an anti-inflammatory effect in different kinds of diseases [5–14]. Liver is one of the major end-organs damaged in the murine aGvHD model, in which the inflammatory response dominates the disease phases [1]. Though there are already many strategies to deal with this kind of disease, they have a rather broad spectrum and affect the overall

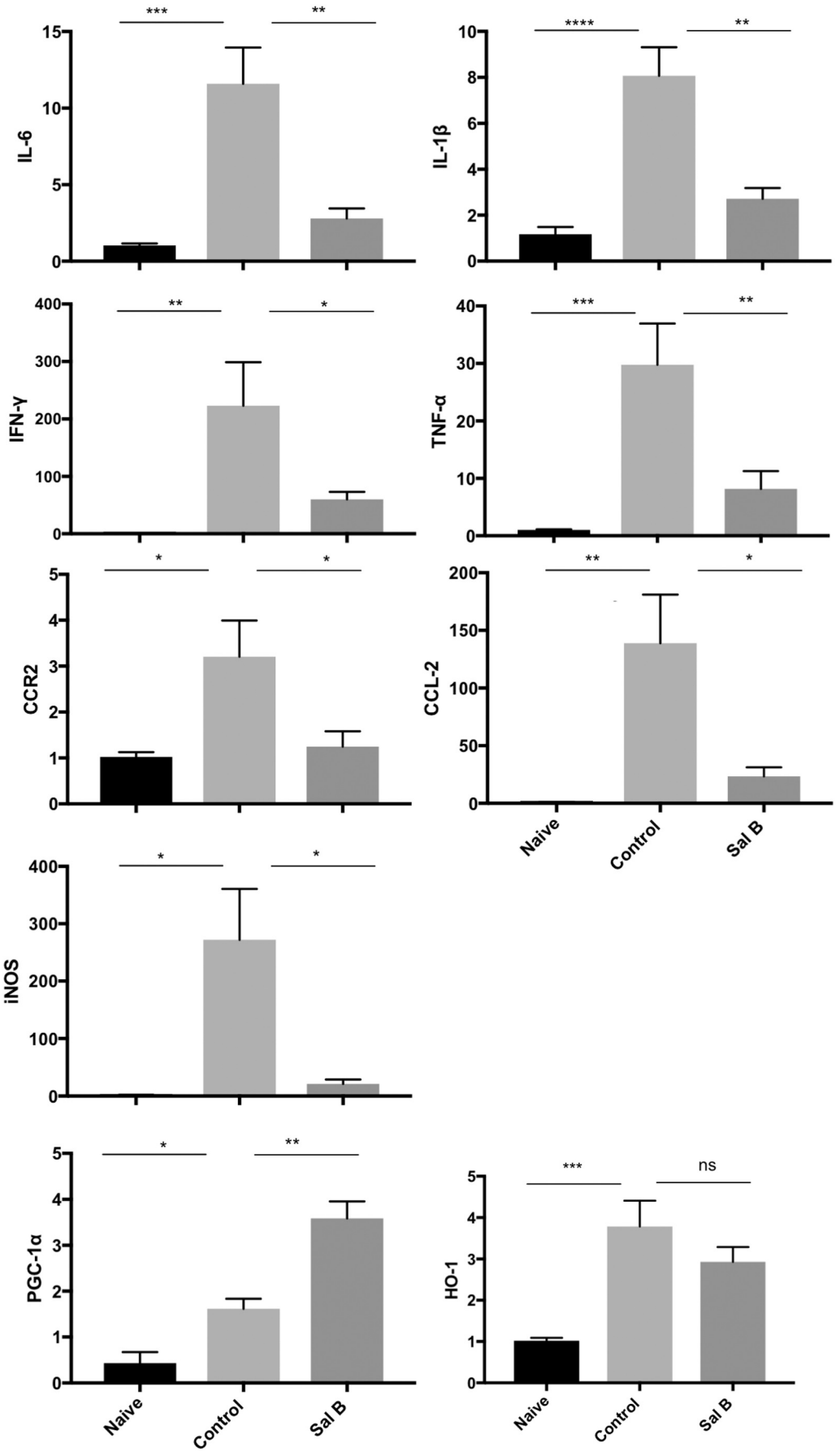


**Fig. 2.** *Sal B ameliorated inflammatory response and decreased M1-type macrophage markers in aGvHD mice*. Liver tissues were collected on day 14. Samples were measured by qRT-PCR as described in Materials and Methods. Sal B suppressed inflammatory responses, such as TNF-α, IL-6, IL-1β, and IFN-γ expression in liver tissue of aGvHD mice. Furthermore, Sal B decreased CCL2, CCR2, iNOS, and TNF-α expression in liver tissue of aGvHD mice. In contrast, Sal B treatment increased PGC-1α, but not HO-1 expression in liver tissue. Data were analyzed and presented as the mean ± SEM. $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$, as compared with the Control group.

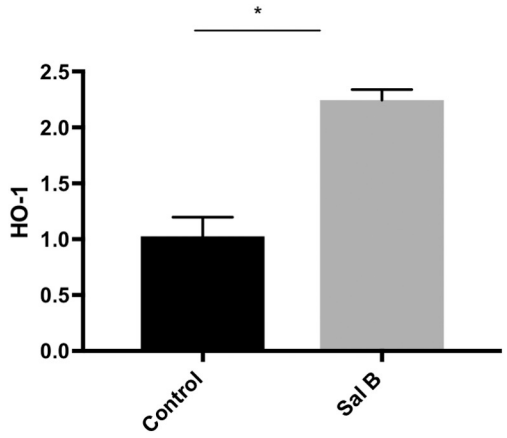


**Fig. 3.** *Sal B increased HO-1 expression in NPCs of aGvHD mice.* NPCs were collected on day 14 isolated from liver and all samples were assayed by qRT-PCR as described in Materials and Methods. Sal B treatment enhanced HO-1 expression in NPCs. Data were analyzed and presented as the mean ± SEM. *$p < .05$ as compared with the Control group.

immune system reconstruction [3]. However, there was a lack of reports that described the inhibitory effect of Sal B on aGvHD, especially in liver pathology. In the present study, we used Sal B in the murine aGvHD model to check whether it has a protective effect from liver damage or not.

Our data showed that Sal B treatment significantly decreased liver histological scoring value compared to aGvHD mice. Sal B treatment also significantly decreased hepatic leakage of enzymes. Furthermore, survival of mice with aGvHD was significantly prolonged (Fig. 1). These data suggested that Sal B ameliorated infiltration of lymphocytes in liver tissue by suppressing expression of inflammatory cytokine(s) and chemokine(s), and decreased levels of liver enzymes in serum by inhibiting apoptosis and necrosis of hepatocytes. Then we focused on the anti-inflammatory effect of Sal B. The expression of proinflammatory cytokines and chemokines, including TNF-α, IL-6, IL-1β, IFN-γ, iNOS, CCL2, and CCR2, in liver tissue was significantly increased in aGvHD mice; these promoted liver damage in aGvHD [2,16,26], whereas Sal B treatment significantly attenuated their expression (Fig. 2). These data clearly demonstrated that the therapeutic effect of Sal B on aGvHD is through the suppression of the inflammatory responses in liver aGvHD by inhibiting proinflammatory cytokine/chemokine expression. In order to further analyze how Sal B suppressed the inflammatory response, we focused on HO-1 and PGC-1α expression in liver; both of them have a protective effect against inflammation and may alter the inflammatory responses as previously reported [5–14,34,38,40]. In addition, high expression of HO-1 reduced aGvHD severity, improved survival rate, and prolonged the survival time [35]. Our data demonstrated that Sal B treatment significantly increased HO-1 expression in NPCs and upregulated PGC-1α expression in liver tissue (Fig. 3). In order to support the concept that Sal B treatment's effect may rely on HO-1 expression, we further used the HO-1 inhibitor, ZnPPIX, whose treatment partially abrogated the prolongation of survival by Sal B (Fig. 1E).

Although our research may provide a novel therapy for aGvHD by administration of Sal B, there are some limitations in our research. For instance, we did not analyze how HO-1 functions in NPCs and how PGC-1α functions in liver tissue. This needs to be further analyzed in future work.

In conclusion, our data showed that Sal B ameliorated liver injury and promoted survival in aGvHD mice. Sal B's protective effect for aGvHD may be through the suppression of the inflammatory response in aGvHD. The therapeutic effect of Sal B may rely on HO-1 production. Our research may offer a novel therapeutic option for aGvHD.

## Acknowledgement

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## Conflict of interest

The authors declare that they have no conflicts of interest.

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