MCTR1 enhances the resolution of lipopolysaccharide-induced lung injury through STAT6-mediated resident M2 alveolar macrophage polarization in mice

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Abstract
Acute respiratory distress syndrome (ARDS) is a fatal disease characterized by excessive infiltration of inflammatory cells. MCTR1 is an endogenously pro-resolution lipid mediator. We tested the hypothesis that MCTR1 accelerates inflammation resolution through resident M2 alveolar macrophage polarization. The mice received MCTR1 via intraperitoneal administration 3 days after LPS stimulation, and then, the bronchoalveolar lavage (BAL) fluid was collected 24 hours later to measure the neutrophil numbers. Flow cytometry was used to sort the resident and recruited macrophages. Post-treatment with MCTR1 offered dramatic benefits in the resolution phase of LPS-induced lung injury, including decreased neutrophil numbers, reduced BAL fluid protein and albumin concentrations and reduced histological injury. In addition, the expression of the M2 markers Arg1, FIZZ1, Remlα, CD206 and Dectin-1 was increased on resident macrophages in the LPS + MCTR1 group. Resident macrophage depletion abrogated the therapeutic effects of MCTR1, and reinjection of the sorted resident macrophages into the lung decreased neutrophil numbers. Finally, treatment with MCTR1 increased STAT6 phosphorylation. The STAT6 inhibitor AS1517499 abolished the beneficial effects of MCTR1. In conclusion, MCTR1 promotes resident M2 alveolar macrophage polarization via the STAT6 pathway to accelerate resolution of LPS-induced lung injury.

Keywords
acute respiratory distress syndrome, alveolar macrophage, lipopolysaccharide, MCTR1, resolution phase of inflammation
Acute respiratory distress syndrome (ARDS) is a devastating clinical syndrome which characterized by an uncontrolled pulmonary inflammation and inflammatory cell accumulation.\(^1\)\(^,\)\(^2\) Investigation of experimental ARDS models has mainly focused on the early inflammation phase,\(^2\) but this strategy has limitations in clinical applications. In contrast, a focus on regulating the resolution phase may provide a new strategy for treatment of ARDS.\(^3\) A previous study indicated that macrophages were necessary to address pulmonary inflammation.\(^4\) Pulmonary inflammation is closely related to two phenotypically distinct cell populations-resident and recruited macrophages.\(^5\)\(^-\)\(^7\) During embryogenesis and self-renew throughout life, resident macrophages accumulate in the lungs\(^8\)\(^,\)\(^9\); recruited macrophages are derive from circulating monocytes, which are transported to the site of inflammation and then mature into macrophages. A recent study showed that resident macrophages suppressed, whereas recruited macrophages promoted, allergic pulmonary inflammation.\(^10\) Another study demonstrated that resident macrophages were not involved in cytokine production, but recruited macrophages seem to be preparative for inflammatory signals with arginine metabolism and cytokine.\(^11\) Therefore, the two populations of macrophages exhibit different capabilities in inflammatory lung disease.

Macrophages can be subclassified into M1 (classically activated or pro-inflammatory) and M2 (alternatively activated or anti-inflammatory) phenotypes.\(^6\)\(^,\)\(^7\)\(^,\)\(^12\) M1 macrophages secrete pro-inflammatory cytokines, which are detrimental to wound healing.\(^13\) M2 macrophages are involved in tissue regeneration, growth, angiogenesis and matrix wound healing, thereby supporting tissue remodelling.\(^14\)\(^-\)\(^16\) Previous studies demonstrated that macrophages transform from a pro-inflammatory M1 phenotype to a pro-resolution M2 phenotype during acute inflammation, which initiates lung repair and restores tissue homoeostasis.\(^17\)\(^,\)\(^18\) Thus, macrophage polarization is important in accelerating the resolution of inflammation and maintaining tissue homoeostasis.

Maresin conjugates in tissue regeneration (MCTR) are a new series of lipid mediators.\(^19\)\(^,\)\(^20\) MCTR1 (13-glutathionyl, 14-hydroxy-docosahexaenoic acid) is obtained from human macrophages and sepsis patients\(^21\) and regulates processes associated with the inflammation-resolution phase, tissue repair and regeneration.\(^22\)\(^,\)\(^23\) MCTR1 not only significantly reduced neutrophil accumulation, but also obviously stimulated macrophage efferocytosis, a key pro-resolution action.\(^24\)\(^,\)\(^25\)

We hypothesis that treatment with MCTR1 at the peak of inflammation promotes the resolution of inflammation in LPS-induced lung injury. Our secondary hypothesis was that accelerated inflammation resolution is associated with resident M2 macrophage polarization. Finally, by investigating the downstream signalling pathways of MCTR1, we determined the effect of STAT6 on resident M2 alveolar macrophage polarization to gain a better understanding of the mechanisms.

### Materials and Methods

#### Materials

MCTR1 was from Cayman Chemical Company. AS1517499 was purchased from MedChemExpress. LPS (Escherichia coli serotype O55:B5) was from Sigma. F4/80-PE-Cyamine7. CD11c-PerCP-Cyamine5.5, CD11b-APC, CD206-PE, Ly-6G-FITC, CD86-PE, Dectin-1-PE, anti-P-STAT6 and total STAT6 (T-STAT6) antibodies were from Invitrogen. Anti-Relmα, Arg-1 and Ym-1 antibodies were from Abcam.

#### Animal preparation

C57BL/6 mice (20-25 g) were from Slac Laboratory Animal. The study was approved by the Animal Studies Ethics Committee of Wenzhou Medical University.

Atomization inhalation of LPS (1 mg/kg) is to establish lung injury model. In MCTR1 group, mice received MCTR1 (0.1 µg/mouse) via intraperitoneal administration. In LPS + MCTR1 group, the mice received MCTR1 via intraperitoneal injection 3 days after LPS stimulation. For the LPS + MCTR1+AS1517499 group, the mice received AS1517499 (10 mg/kg) via intraperitoneal administration 2 hours before MCTR1 intervention. After anesthetization with sodium pentobarbital (60 mg/kg, i.p.), BAL fluid was collected on Day 4.

#### Pathological studies

For pathological studies, the trachea was cannulated with a tube, and the lungs were infused with 4% paraformaldehyde at 25 cm H2O (2.4 kPa) for 1 hour. The lungs were removed with the trachea securely tied with surgical sutures under a pressure of 25 cm H2O, fixed in 4% paraformaldehyde for an additional 24 hours, embedded in paraffin and stained with haematoxylin and eosin for light microscopy analysis. Acute lung injury score was based on alveolar congestion, alveolar haemorrhage, alveolar wall/hyaline membrane thickness and inflammatory cell accumulation. 0 = no injury; 1 = slight injury (25%); 2 = moderate injury (50%); 3 = severe injury (75%); and 4 = very severe injury (almost 100%).

#### Flow cytometry

BAL cells were cultured with variety antibodies for 20 minutes and FACS lysing solution for 10 minutes, then centrifuged at 400 g for 5 minutes and resuspended in PBS to analyse using FACS Calibur (Beckman Coulter). Resident macrophages were defined as F4/80+CD11b+CD11c+ and recruited macrophages were labelled as F4/80+CD11b+CD11c- as previously described.\(^26\)
2.5 | Resident macrophages depletion

Clodronate liposomes (5 mg/mL, 50 μL) were intratracheal instillation to deplete the resident macrophage. PBS liposomes were used as control. Three days later, the mice underwent aerosol inhalation with LPS (1 mg/kg). After another 3 days, the mice received MCTR1 via intraperitoneal administration. Then, BAL fluid was collected.

2.6 | Depletion of recruited macrophages

Recruited macrophages were depleted by a single caudal vein injection of clodronate liposomes (200 μL) 8 hours before the administration of LPS. Three days after 1 mg/kg LPS administration, the mice received MCTR1 via intraperitoneal injection. Then, BAL fluid was harvested.

2.7 | Cell sorting and reinjection

Cells were sorted using a 100 μm nozzle size and then directly into tubes containing RPMI by a CytoFLEX flow cytometer (Beckman Coulter). The sorted resident or recruited macrophages (1 × 10⁶) were reinjected intratracheally into the lung. The mice were randomized into five groups (n = 6-8): LPS group, recruited Mø group, resident Mø group, MCTR1 recruited Mø group and MCTR1 resident Mø group. The resident and recruited macrophages were sorted after LPS stimulation for 3 days. For the recruited, resident Mø and LPS groups, the mice received sorted resident macrophages, recruited macrophages or an equivalent volume of PBS via intratracheal injection. Next, MCTR1 was administered on Day 3 after LPS administration, and resident and recruited macrophages were sorted on Day 4. Then, the cells were reinjected into the lung to establish the MCTR1 resident Mø and resident Mø groups. Twenty-four hours later, BAL fluid was collected for neutrophil count analysis.

2.8 | Western blotting

Proteins were extracted using RIPA lysis buffer, and protein concentration was measured by a protein assay kit. 10% sodium-dodecyl sulphonate polyacrylamide gel was used to separate the protein. After primary and secondary antibodies cultured, the protein bands were measured by using a UVP gel imaging system.

2.9 | ELISA

The BAL fluid from individual mice was centrifuged, and the supernatant was collected. The protein, albumin, IL-4, IL-13 and IL-1β levels in the BAL fluid were determined. Furthermore, IL-4, IL-13 and IL-1β concentrations in the lung homogenate were also detected by ELISA (R&D Systems).

2.10 | Statistical analysis

The data were expressed as the mean ± SD. All data were analysed by one-way ANOVA followed by Tukey’s post hoc test for multiple comparisons. Significance was determined at P < .05. Statistical analyses were performed using Prism 6.0 software.

3 | RESULTS

3.1 | MCTR1 accelerated the resolution of inflammation in LPS-induced lung injury

The experiment was designed as indicated in Figure 1A. We first determined neutrophil changes by using an LPS-induced lung injury model. Neutrophil numbers peaked at 72 hours and then gradually decreased until 144 hours (Day 6). Between 72 hours (Tmax) and 92 hours (T50), total neutrophil numbers reduced from 3.2 × 10⁶ (Ψmax: maximal PMN number) to 1.6 × 10⁶ (R50: 50% reduction in neutrophils). For a direct comparison, this period of neutrophilic loss from the exudates (ie 13-20 hours) is termed the resolution interval (Ri) (Figure 1B). MCTR1 reduced the T50 from 92 to 85 hours, thus shortening the Ri from 20 to 13 hours compared with that of the LPS group (Figure 1B).

The number of neutrophils decreased most quickly on Day 4 after administration of MCTR1 compared with that of the LPS group (Figure 1C,D). In addition, both the protein and albumin concentrations in the BAL fluid were reduced in the LPS + MCTR1 group compared with those of the LPS group (P < .05; Figure 1E,F). However, there was no significant difference between the CTR and MCTR1 groups (Figure 1D-F; P > .05).

Furthermore, the lung architecture in the LPS group was obviously damaged, with inflammatory cell infiltration, interstitial oedema, damaged pulmonary alveoli structures and haemorrhaging. All morphological changes were less pronounced in the LPS + MCTR1 group (Figure 1G). However, there was no significant difference between the CTR and MCTR1 groups (P > .05) (Figure 1G). Acute lung injury scores were quantified in parallel with the pathophysiological changes (Figure 1H). The bodyweight recovered faster in the LPS + MCTR1 group than in the LPS group on Day 4 (P < .05 but not on Day 3 (P > .05; Figure 1I)). (%weight change = (baseline-present)/baseline).

3.2 | MCTR1 enhanced M2 macrophage polarization

The number of macrophages in BAL fluid increased and peaked on Day 3 in LPS-induced lung injury (Figure 2A). CD206 expression in BAL macrophages was decreased on Day 2 and then gradually
increased until Day 14 after LPS administration (Figure 2B). The macrophages were most prominently decreased on Day 4; therefore, the BAL fluid was collected on Day 4 in the subsequent experiment.

The mean fluorescence intensity (MIF) of CD206 in BAL macrophages in the LPS + MCTR1 group was enhanced compared with that in the LPS group (P < .05; Figure 2C). The expression of three M2 markers, Arg-1, Ym-1 and Relmα, in lung tissues was increased in the LPS + MCTR1 group compared with that of the LPS group (P < .05; Figure 2D-G).

3.3 MCTR1 promoted M2 polarization of resident but not recruited macrophages

Resident and recruited macrophages were labelled with F4/80⁺CD11b⁺CD11c⁻ and F4/80⁺CD11b⁺CD11c⁺, respectively. We sorted resident and recruited macrophages from the BAL fluid of C57BL/6 mice (Figure 3A). The number of recruited macrophages increased after LPS stimulation, peaked on day 3 and then declined gradually to normal levels until Day 14 (Figure 3B). The resident
Macrophages remained largely constant during the course of inflammation (Figure 3B). CD206 was mainly expressed on resident macrophages, decreased during the first 2 days and then increased from Day 4 to Day 14 after LPS stimulation (Figure 3C). The percentage of CD206 cells among recruited macrophages increased after LPS stimulation and reached a maximum on Day 4 and then declined slowly to normal levels until Day 14 (Figure 3C).

In addition, compared with the LPS group, the MIFs of CD206 and Dectin-1 on resident macrophages in the LPS + MCTR1 group were increased ($P < .05$), but there was no difference between the LPS and LPS + MCTR1 groups ($P > .05$; Figure 3D,E).

### 3.4 MCTR1 accelerated the resolution of inflammation via resident macrophages

Recruited macrophages were depleted by clodronate liposome stimulation (Figure 4A,B).
**Figure 4** MCTR1 accelerated the resolution of inflammation by regulating resident macrophages. The different populations of macrophages were depleted by injecting clodronate liposomes, and then, MCTR1 (0.1 µg/mouse) was administered 3 d after LPS (1 mg/kg) stimulation. BAL fluid was collected on Day 4. The recruited macrophages were depleted by injecting 200 µL clodronate liposomes through the tail vein for 8 h (A, B), and then, macrophage (C), neutrophil (D) and protein levels (E) in the BAL fluid were detected. The resident macrophages were depleted by intratracheal administration of 50 µL clodronate liposomes for 3 d (E-G), and then, the macrophage (H), neutrophil (I) and protein levels (J) in the BAL fluid were measured. The data are presented as the mean ± SEM. n = 6-8. *P < .05, **P < .01, ***P < .001, ****P < .000
MCTR1 reduced the number of recruited macrophages compared with the LPS + PBS liposome group \((P < .05; \text{Figure 4C})\). The recruited macrophages were depleted by clodronate liposome intervention after LPS stimulation with or without MCTR1 \((P < .05)\), indicating that our model was successfully established (Figure 4C). The recruited macrophages were depleted by clodronate liposome intervention after LPS stimulation with or without MCTR1 \((P < .05)\), indicating that our model was successfully established (Figure 4C). The neutrophil numbers and BAL protein reduced in the LPS + MCTR1 group compared with those of the LPS group after clodronate liposome administration to deplete recruited macrophages \((P < .05; \text{Figure 4D,E})\).

MCTR1 also decreased BAL protein alone in the absence of clodronate liposomes, but MCTR1 was more effective in the presence of clodronate (Figure 4E).

In addition, after intratracheal clodronate liposome administration (Figure 4F,G), the resident macrophages were reduced compared with those of the PBS liposome group \((P < .05; \text{Figure 4H})\). The LPS + MCTR1+clodronate liposome group had fewer resident macrophages compared with those of the LPS + MCTR1+PBS liposome group \((P < .05)\), suggesting that clodronate liposomes alone reduced the resident macrophages and that there was no additional effect of MCTR1 in this group (Figure 4H). Compared with the PBS liposome group, the neutrophil numbers and BAL protein were increased in the clodronate liposome group \((P < .05; \text{Figure 4I,J})\), but there were no significant differences between the LPS + MCTR1 and LPS groups after clodronate liposome stimulation \((P > .05; \text{Figure 4I,J})\).

3.5 | Reinjected resident macrophages accelerated the resolution of inflammation

Furthermore, sorted resident or recruited macrophages were reinjected into the lung (Figure 5A). The resident macrophages exhibited a smooth nuclear shape and morphology similar to that of mature macrophages, and the recruited macrophages had irregular contours and morphology, resembling less mature macrophages (Figure 5B). Neutrophils were reduced in the resident Mø group compared with those in the LPS group \((P < .05)\), and neutrophils were decreased in the MCTR1 resident Mø group compared with those in the resident Mø group \((P < .05; \text{Figure 5C})\). However, there were no significant changes in neutrophil numbers in the LPS, recruited Mø or MCTR1-recruited Mø groups \((P > .05; \text{Figure 5C})\).

3.6 | MCTR1 promoted M2 macrophage polarization via the STAT6 pathway, not IL-4 and IL-13

It is well established that IL-4 and IL-13 play central roles in M2 macrophage polarization. However, in the present study, we found that there was no significant difference in IL-4 and IL-13 concentrations in lung tissues or BAL fluid between the LPS and LPS + MCTR1 groups \((P > .05; \text{Figure 6A-D})\). However, we found that LPS administration increased p-STAT6 protein levels in resident macrophages compared with those of the CTR group \((P < .05; \text{Figure 6E,F})\). Moreover, p-STAT6 protein expression in resident macrophages was increased in the LPS + MCTR1 group compared with that of the LPS group \((P < .05; \text{Figure 6E,F})\). The increased protein level of CD206, Arg-1, Ym-1 and Relmα in resident macrophages in the BAL in the LPS + MCTR1 group was abrogated by AS1517499, a STAT6 inhibitor \((P < .05; \text{Figure 6G-L})\).

3.7 | The pro-resolution effect of MCTR1 on lung injury inflammation was abolished by a STAT6 inhibitor

The benefit effect of MCTR1 on morphological changes was abolished by AS1517499 (Figure 7A). The acute lung injury score in the LPS + MCTR1+AS1517499 group was higher than that in the LPS + MCTR1 group \((P < .05; \text{Figure 7B})\). The neutrophil numbers were much higher in the LPS + MCTR1+AS1517499 group than in the LPS + MCTR1 group \((P < .05; \text{Figure 7C})\). The BFA protein concentration in the LPS + MCTR1+AS1517499 group was increased compared with the LPS + MCTR1 group \((P < .05; \text{Figure 7D})\).
In this study, we found that post-treatment with MCTR1 on Day 3, at peak inflammation, decreased neutrophil numbers, BAL protein and albumin in mice 4 days after LPS-induced lung injury. In addition, MCTR1 markedly promoted resident M2 macrophage polarization to accelerate the resolution of inflammation. In addition, MCTR1 increased STAT6 phosphorylation. AS1517499, a STAT6 inhibitor, abolished resident M2 macrophage polarization and the protective effects of MCTR1. These results indicate that MCTR1 promotes resident M2 macrophage polarization to accelerate the resolution of inflammation and was mainly mediated by the STAT6 pathway.

Resolution of inflammation is important for patient survival. Resolution of inflammation is characterized by the release of pro-resolving mediators and the removal of infiltrated leukocytes. In the present study, we introduced a set of resolution indices to define Ri as the time interval from the recorded maximum neutrophil infiltration point to the 50% reduction point. We showed that Ri was 20 hours in an LPS-induced lung injury model. After treatment with MCTR1, the Ri was 13 hours, suggesting that MCTR1 shortened the Ri. MCTR1 also reduced BAL protein and albumin, attenuated lung injury and enhanced mouse weight recovery 24 hours later. MCTR1 obviously promoted the resolution of LPS-induced ARDS.

It is well known that macrophages act as critical effectors that induce inflammation. In ARDS, macrophages, including M1 (pro-inflammatory) and M2 (anti-inflammatory) macrophages, are present in the BAL fluid. M2 macrophage polarization is a key step in the resolution of ARDS inflammation. Here, we demonstrated that the total number of macrophages peaked on Day 3 and then gradually declined, but the percentage of M2 macrophages decreased during the first 2 days and then gradually increased until Day 14. Treatment with MCTR1 at the peak of inflammation up-regulated CD206, Arg-1, Ym-1 and Relmα protein expression in LPS-induced lung injury, indicating that MCTR1 promoted M2 polarization of macrophages.

Two populations of macrophages, resident alveolar macrophages and recruited macrophages from circulating monocytes, participate in the pathogenesis of ARDS. Next, we investigated the effects of MCTR1 on M2 polarization of the two types of macrophages. We found that recruited macrophages were increased and peaked on Day 3 and then recovered to the steady state on Day 14 after LPS exposure, but resident alveolar macrophages were stabilized during these days, suggesting that after LPS stimulation, a large number of recruited macrophages infiltrate the lung to participate in initiating inflammation and then are reduced in the resolution phase, but the number of resident alveolar macrophages changed very little, which was consistent with a previous study. The percentage of CD206 cells decreased among resident...
macrophages until Day 4 and then rose back to a level similar to that of Day 0 from days 6-14 after LPS stimulation, suggesting that M2 macrophages were mainly derived from resident macrophages. In addition, we also found that treatment with MCTR1 up-regulated the MIF of CD206 and Dectin-1 expression on resident macrophages but not recruited macrophages, suggesting that M2 macrophages mainly originated from resident macrophages during the resolution phase and that MCTR1 promoted resident M2 polarization.

We further investigated the effects of MCTR1 on the two populations of macrophages. Clodronate liposomes were used to deplete the different populations of macrophages. MCTR1 also decreased neutrophil numbers and BAL protein expression when recruited macrophages were depleted. However, MCTR1 had no effect on neutrophil numbers or BAL protein expression when resident macrophages were depleted. These results indicated that MCTR1 accelerated the resolution of inflammation through resident macrophages.

To further clarify the importance of resident macrophages in the resolution phase, sorted resident and recruited macrophages were reinjected into the lung. We found that neutrophil numbers were decreased after resident but not recruited macrophages were reinjected into the lung. In addition, the neutrophils decreased much more in the MCTR1 treatment with resident macrophage group. These results suggest that MCTR1 promotes resident M2 macrophage polarization to accelerate the resolution of inflammation.

The mechanisms by which MCTR1 promote resident M2 macrophage polarization to accelerate inflammation resolution in mice remain to be clarified. A previous study showed that IL-4 and IL-13 are involved in macrophage polarization, but we found that the IL-4 and IL-13 levels were unchanged after treatment with MCTR1 in LPS-induced mice, indicating that MCTR1 regulates macrophage polarization to promote the resolution of inflammation independent of IL-4 and IL-13.

Activation of STAT6 is a key signalling pathway in macrophage function. Recent work has demonstrated that STAT6-dependent M2 protein upregulation is important in accelerating resolution in LPS-induced lung injury. Consistently, we found that treatment with MCTR1 increased STAT6 phosphorylation without affecting total STAT6 expression in resident macrophages. The MCTR1-mediated increase in CD206, Arg-1, Ym-1 and Relmα protein expression in resident macrophages and protection against lung injury were abrogated by the STAT6 inhibitor AS1517499, suggesting that MCTR1-promoted resident M2 macrophage polarization was dependent on the STAT6 pathway.

In summary, MCTR1 decreased neutrophil numbers and BAL protein and albumin concentrations, enhanced inflammation resolution and attenuated lung injury by promoting resident M2 macrophage polarization, which was mediated by the STAT6 pathway. Our findings reveal that MCTR1 may be a new treatment strategy for ARDS.
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CONFLICT OF INTEREST

The other authors declared no conflict of interest.

AUTHOR CONTRIBUTIONS

Qian Wang and Hua-Wei Zhang designed the research study and performed the research. Hong-Xia Mei, Yang Ye, Hao-Ran Xu and Shu-Yang Xiang collated the data and carried out data analyses. Qian Yang, Sheng-Xing Zheng and Fang Gao Smith contributed to drafting the manuscript. Sheng-Wei Jin revised the paper. All authors have read and approved the final submitted manuscript.

DATA AVAILABILITY STATEMENT

I confirm that the article contains a Data Availability Statement even if no data are available. I confirm that I have included a citation for available data in my references section.

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