MEDICAL SCIENCE MONITOR

ANIMAL STUDY

e-ISSN 1643-3750
© Med Sci Monit, 2019; 25: 4450-4456
DOI: 10.12659/MSM.914026

Received: 2018.11.07
Accepted: 2018.12.11
Published: 2019.06.15

Treatment with Recombinant Interleukin-15 (IL-15) Increases the Number of T Cells and Natural Killer (NK) Cells and Levels of Interferon-γ (IFN-γ) in a Rat Model of Sepsis

Authors' Contribution:
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Data Collection B
Statistical Analysis C
Data Interpretation D
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Source of support: Departmental sources

Background: This study aimed to investigate the effects of treatment with recombinant interleukin-15 (IL-15) on T cells, natural killer (NK) cells, and interferon-γ (IFN-γ) on the immune response in a rat cecal ligation and perforation model of sepsis.

Material/Methods: Sprague-Dawley rats (n=120) were divided into four groups (n=30). A rat model of clinical sepsis was created using cecal ligation and perforation, and 109 rats successfully developed sepsis. Rats were then injected intraperitoneally with 0.5, 1.0, and 1.5 μg of recombinant rat IL-15 or saline. Survival was determined, and the numbers of T cells and NK cells, and the expression levels of IL-15 and IFN-γ were detected in the peripheral blood of rats in each group at 24 h and 48 h.

Results: The levels of IL-15 and IFN-γ, as well as the numbers of T cells and NK cells, were significantly increased in the IL-15-treated groups compared with the control group at both 24 h and 48 h ($P<0.05$). Levels of IL-15 and IFN-γ were significantly increased in the IL-15-treated groups at 48 h compared with 24 h in the control group. Levels of IL-15, the numbers of T cells and NK cells, and the levels of IFN-γ in peripheral blood were significantly lower at 48 h when compared with 24 h ($P<0.05$).

Conclusions: In a rat model of sepsis, treatment with recombinant IL-15 significantly increased T cell and NK cell numbers, and levels of IFN-γ, and prolonged the survival of rats with sepsis.

MeSH Keywords: Antisepsis • Asepsis • Lemierre Syndrome

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/914026

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Background

Sepsis is a systemic inflammatory response that is triggered by infection and continues to be a topic of research interest due to its clinical importance and high patient mortality [1–3] Worldwide, there are more than 30 million cases of severe sepsis each year resulting in five million annual deaths [4]. In the United States, there are approximately 800,000 annual cases of sepsis, with the number of cases continuing to rise at an annual rate of 6.1% [2,3]. It has been reported that mortality rates from sepsis have recently surpassed mortality rates from sudden death from cardiovascular disease, including myocardial infarction, and that sepsis is now the main cause of death in non-cardiac patients in intensive care units [5]. On the basis of these findings, there is a need for continued research to improve methods of diagnosis and treatment. Recently, experimental studies on sepsis have been continuously innovative, and there have been significant achievements in anti-infective treatment and organ function support technologies [6,7]. However, the mortality rate from sepsis can still be as high as 64.3% and, together with increasingly expensive treatment costs and the increasing use of medical resources, sepsis is a serious condition that in terms of patient quality of life, morbidity, and mortality and healthcare costs [8].

The underlying pathogenesis of sepsis remains unclear. However, it has been shown that sepsis results from immune dysfunction and infection [9]. T cells are intrinsic components of the human immune response and mature T cells can be recycled through the lymphatic vessels and peripheral circulation, exerting roles in cellular immunity and immune regulation [10]. Natural killer (NK) cells are also important in cellular immunity and microbial defense [11]. Some studies have shown that NK cells are involved in antitumor [12], antiviral [13], and immunoregulatory responses [14], and NK cells also participate in the development of hypersensitivity and autoimmune disease. NK cells can identify and kill target cells [15]. Interferon-γ (IFN-γ) is produced by activated T cells and NK cells and is an important immune regulator *in vivo* [16]. Interleukin-15 (IL-15) is also produced by macrophages, and IL-15 receptors are widely distributed on the surface of immune cells [17]. IL-15 has multiple immune functions and promotes the proliferation of T cells [18], and NK cells [19].

Therefore, this study aimed to investigate the effects of treatment with recombinant rat IL-15 on T cells, NK cells, and IFN-γ on the immune response in a rat cecal ligation and perforation model of sepsis and to investigate the effects of recombinant IL-15 treatment on the survival of rats with sepsis.

Material and Methods

The rat model of sepsis and the experimental design

A total of 120 specific pathogen-free (SPF) grade healthy male Sprague-Dawley rats (Nanjing Junke Biotechnology, Nanjing, Jiangsu, China) with an average body weight of 154.2±10.3 g were randomly divided into four groups, A, B, C, and an untreated sepsis group with 30 rats in each group. The experimental animals underwent cecal ligation and puncture (CLP) to create the model of sepsis, as previously described [20]. There were 28 successful rat models of sepsis in group A, 27 successful rat models of sepsis in group B, 26 successful rat models of sepsis in group C, and 28 successful rat models of sepsis in the untreated sepsis group. In total, 109 successful sepsis rat models were created with a success rate of 90.8%. All the rats that did not develop sepsis were excluded from the study.

The experimental animal procedures used were approved by the Animal Care and Use Committee of Fudan University Shanghai Cancer Center, and followed the guidelines of the National Institute of Health. Rats in groups A, B, C, and the untreated sepsis group were injected intraperitoneally with 0.5 μg, 1.0 μg, and 1.5 μg of IL-15, or normal saline, 1 h after the creation of the model of sepsis. A total of 10 rats were randomly selected from each group after injection for survival analysis, and the remaining animals were used in other experiments.

Reagents

Recombinant rat IL-15 was provided by PeproTech (Suzhou, Jiangsu,China), phycoerythrin (PE)-conjugated anti-mouse CD3 was obtained from Hengfei Biotechnology (Shanghai, China), fluorescein isothiocyanate (FITC)-conjugated anti-mouse NK-1.1 was obtained from Haoran Biotechnology (Shanghai, China), a rat IL-15 enzyme-linked immunoassay (ELISA) kit was obtained from Ruiqi Biotechnology (Shanghai, China), and a rat interferon-γ (IFN-γ) ELISA kit was obtained from Ruite Biotechnology (Guangzhou, Guangdong, China). A CytoFLEX flow cytometer was used for flow cytometry analysis (Beckman Coulter Trade, Shanghai, China).

ELISA detection of IL-15 and IFN-γ

In addition to the survival experiment, peripheral blood (0.5 mL) was sampled through the caudal vein in each group at 24 h and 48 h after intraperitoneal injection of recombinant IL-15 or saline, left at room temperature for 10 min and centrifuged at 3000 rpm for 20 min. The supernatant was carefully collected. If a precipitate was found in the collected supernatant, the specimen was centrifuged again. Serum levels of IL-15 and IFN-γ were measured by ELISA according to the manufacturer's instructions. Each assay was performed in triplicate.

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Table 1. IL-15 content (pg/ml) in tail vein blood at 24 h and 48 h in each group.

Time	Group A	Group B	Group C	Group D	F-value	P-value
24 h	56.38±10.22*	89.54±11.63*	124.66±10.95	42.11±8.15*	216.3	0.0001
48 h	79.72±12.85#	106.24±16.75#	153.26±6.15	29.36±9.66#	313.2	0.0001
t	6.031	3.377	9.109	4.280	–	–
P-value	0.0001	0.0019	0.0001	0.0001	–	–

* Represents a statistically significant difference from Group C 24 h, P<0.05; # Represents difference between Group C 48 h was statistically significant, P<0.05.

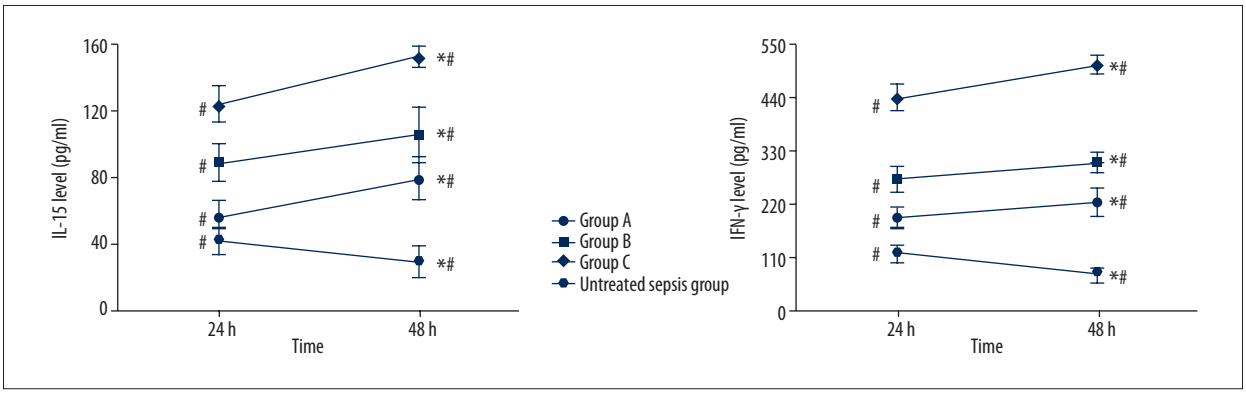

Figure 1. Protein levels of IL-15 in peripheral blood of rats with sepsis at 24 and 48 h after treatment with IL-15. The figure shows the trends of IL-15 levels at 24 and 48 h for each group. * Represents the difference between each group that was statistically significant at 24 h (P<0.05); # Represents statistically significant differences between the groups at the same time (P<0.05).

T cell and NK cell detection

In addition to the survival experiment, peripheral blood (0.5 mL) was sampled through the caudal vein in each group at 24 and 48 h after intraperitoneal injection of recombinant IL-15 or saline. After depletion of the red blood cells by red blood cell lysate, cells were rinsed three times with phosphate-buffered saline (PBS) (pH 7.4) and resuspended in PBS with 0.5% bovine serum albumin (BSA). T cells and NK cells were labeled with PE-conjugated anti-mouse CD3 and FITC-conjugated anti-mouse NK1.1, respectively. T cells and NK cells were analyzed using a CytoFLEX flow cytometer (Beckman Coulter Trade, Shanghai, China). The experiments were performed in triplicate.

Statistical analysis

Data were analyzed using SPSS version 22.0 software (Bomai Information Technology, Guangzhou, China). The measurement data were represented as the mean±standard deviation (SD). The difference between the two groups was compared using the t-test, and multiple groups were compared using analysis of variance (ANOVA). Kaplan–Meier survival curves were plotted and the log-rank method was used to determine differences between the survival curves.

Results

Levels of IL-15 in peripheral blood from rats with sepsis after treatment with recombinant rat IL-15

The protein levels of IL-15 in the peripheral blood of rats at 24 h and 48 h after intraperitoneal injection of recombinant IL-15 or saline were measured by enzyme-linked immunoassay (ELISA). At 24 h and 48 h, the serum levels of IL-15 in groups A, B, and C (56.38±10.22 *vs.* 79.72±12.85, 89.54±11.63 *vs.* 106.24±16.75, and 124.66±10.95 *vs.* 153.26±6.15 pg/mL, respectively) were significantly increased when compared with the serum levels of IL-15 in the untreated sepsis group (42.11±8.15 *vs.* 29.36±9.66 pg/mL) (P<0.05). In groups A, B, and C, the serum levels of IL-15 were significantly increased at 48 h when compared with the levels at 24 h. In the untreated sepsis group, the serum levels of IL-15 were significantly lower at 48 h when compared with the levels at 24 h (P<0.05). The serum levels of IL-15 at 24 h and 48 h were highest in group C, followed by group B, and the differences were statistically significant (P<0.05) (Table 1, Figure 1).

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Table 2. IFN-γ levels (pg/ml) in tail vein blood at 24 h and 48 h in each group.

Time	Group A	Group B	Group C	Group D	F-value	P-value
24 h	194.21±21.54*	271.21±26.83*	441.63±29.44	119.23±19.42*	535.3	0.0001
48 h	226.34±29.84#	307.69±21.48#	508.21±19.35	74.36±15.44#	1114	0.0001
t	3.704	4.376	7.560	7.673	–	–
P-value	0.0007	0.0001	0.0001	0.0001	–	–

* Represents a statistically significant difference from Group C 24 h, P<0.05; # Represents difference between Group C 48 h was statistically significant, P<0.05.

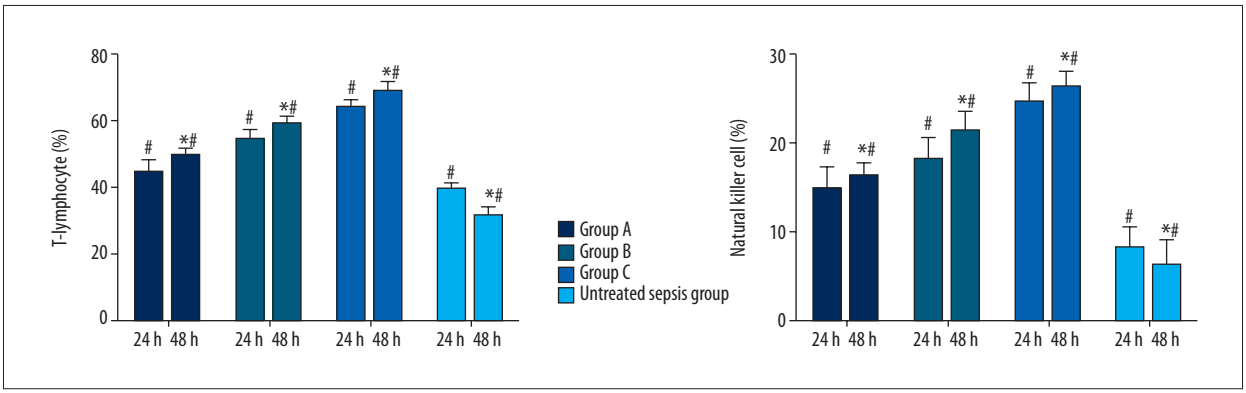

Figure 2. Protein levels of IFN-γ in peripheral blood of rats with sepsis at 24 and 48 h after treatment with IL-15. The figure shows the trends of IFN-γ levels at 24 and 48 h for each group. * Represents the difference between each group that was statistically significant at 24 h (P<0.05); # Represents the statistically significant difference between the groups at the same time (P<0.05).

Levels of IFN-γ in peripheral blood from rats with sepsis after treatment with recombinant rat IL-15

ELISA was used to detect the serum levels of IFN-γ in rats with sepsis at 24 and 48 h after intraperitoneal injection of IL-15 or saline. The serum levels of IFN-γ at 24 h and 48 h in groups A, B, and C (194.21±21.54 *vs.* 226.34±29.84, 271.21±26.83 *vs.* 307.69±21.48, 441.63±29.44 *vs.* 508.21±19.35 pg/mL, respectively) were significantly increased when compared with those in the untreated sepsis group (119.23±19.42 *vs.* 74.36±15.44 pg/mL) (P<0.05). The serum levels of IFN-γ in groups A, B, and C were significantly increased at 48 h when compared with the serum levels at 24 h. In the untreated sepsis group, the serum levels of IFN-γ were significantly reduced at 48 h when compared with the levels at 24 h (P<0.05). The serum IFN-γ levels at 24 and 48 h were highest in group C, followed by group B. The differences were statistically significant (P<0.05) (Table 2, Figure 2).

The percentage of T cells in peripheral blood from rats with sepsis after treatment with recombinant rat IL-15

The percentage of T cells in the peripheral blood at 24 and 48 h in each group was detected. The percentage of T cells in peripheral blood at 24 and 48 h in groups A, B, and C (44.14±3.88 *vs.* 49.16±2.25, 54.32±3.03 *vs.* 58.74±2.64, and 63.74±2.47 *vs.* 68.22±3.31%, respectively) were significantly increased when compared with the untreated sepsis group (39.32±1.65 *vs.* 31.28±2.96%) (P<0.05). The percentage of T cells in the peripheral blood in groups A, B, and C were significantly increased at 48 h compared with 24 h but were significantly lower at 48 h than at 24 h in the untreated sepsis group (P<0.05). The percentages of T cells in peripheral blood was highest at 24 h and 48 h in group C, followed by group B, and the differences were statistically significant (P<0.05) (Table 3, Figure 3).

The numbers of NK cells in peripheral blood from rats with sepsis after treatment with recombinant rat IL-15

Flow cytometry was used to detect the percentage of NK cells in the peripheral blood at 24 h and 48 h in each group. The percentage of NK cells in groups A, B, and C (14.89±2.46 *vs.* 16.33±1.26, 18.22±2.48 *vs.* 21.31±2.37, and 24.65±2.14 *vs.* 26.28±1.75%, respectively) were significantly increased when compared with the control group (8.15±2.33 *vs.* 6.33±2.72%) (P<0.05). The percentage of NK cells in the peripheral blood in groups A, B, and C were significantly increased at 48 h

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Table 3. T-cell levels in tail vein blood at 24 h and 48 h in each group (%).

Time	Group A	Group B	Group C	Group D	F-value	P-value
24 h	44.14±3.88*	54.32±3.03*	63.74±2.47	39.32±1.65*	240.8	0.0001
48 h	49.16±2.25#	58.74±2.64#	68.22±3.31	31.28±2.96#	543.7	0.0001
t	4.749	4.535	4.339	10.07	–	–
P-value	0.0001	0.0001	0.0001	0.0001	–	–

* Represents a statistically significant difference from Group C 24 h, P<0.05; # Represents difference between Group C 48 h was statistically significant, P<0.05.

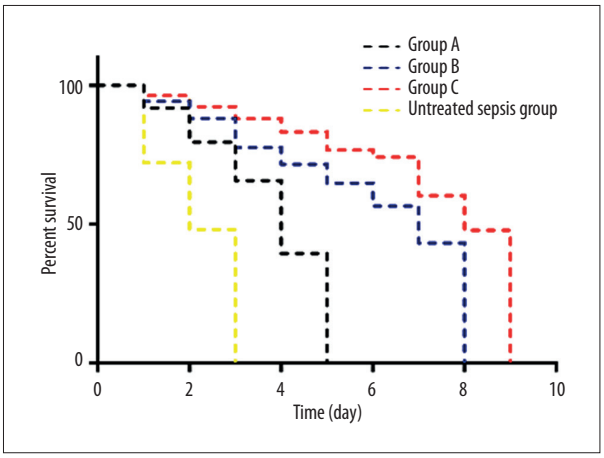

Figure 3. Numbers of T cells in peripheral blood of rats with sepsis at 24 and 48 h after treatment with IL-15. The figure shows the trends of T cell percentages at 24 and 48 h for each group. * Represents the difference between each group that was statistically significant at 24 h (P<0.05); # Represents the statistically significant difference between the groups at the same time (P<0.05).

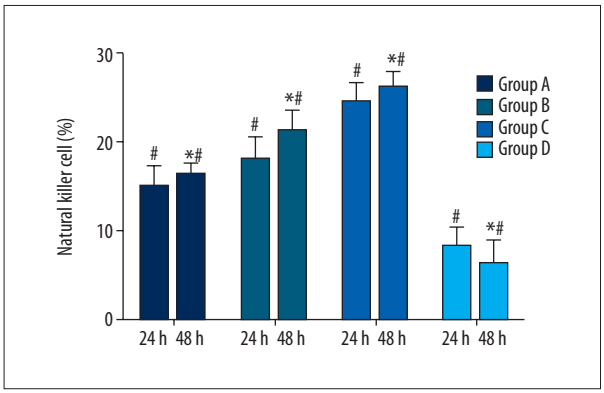

Figure 4. Numbers of NK cells in peripheral blood of rats with sepsis at 24 and 48 h after treatment with IL-15. The figure shows the trends of NK cell percentages at 24 and 48 h in each group. * Represents the difference between each group that was statistically significant 24 h (P<0.05); # Represents the statistically significant difference between the groups at the same time (P<0.05).

Table 4. NK cell levels of tail vein blood at 24h and 48h in each group (%).

Time	Group A	Group B	Group C	Group D	F-value	P-value
24 h	14.89±2.46*	18.22±2.48*	24.65±2.14	8.15±2.33*	144.1	0.0001
48 h	16.33±1.26#	21.31±2.37#	26.28±1.75	6.33±2.72#	281.3	0.0001
t	2.210	3.714	2.359	2.156	–	–
P-value	0.0339	0.0008	0.0251	0.0383	–	–

* Represents a statistically significant difference from Group C 24 h, P<0.05; # Represents difference between Group C 48 h was statistically significant, P<0.05.

compared with 24 h. The percentage of NK cells in the untreated sepsis group was significantly lower at 48 h compared with 24 h (P<0.05). The percentage of NK cells in the peripheral blood were highest at 24 h and 48 h in group C, followed by group B, and the differences were statistically significant (P<0.05) (Table 4, Figure 4).

The survival of 10 randomly selected rats with sepsis after treatment with recombinant rat IL-15

The survival of rats in groups A, B, and C (4.3±1.4, 6.8±1.2, 7.1±1.8 days, respectively) was significantly increased when compared with survival in the untreated sepsis group (2.1±0.6 days), as determined by the Kaplan-Meier and log-rank

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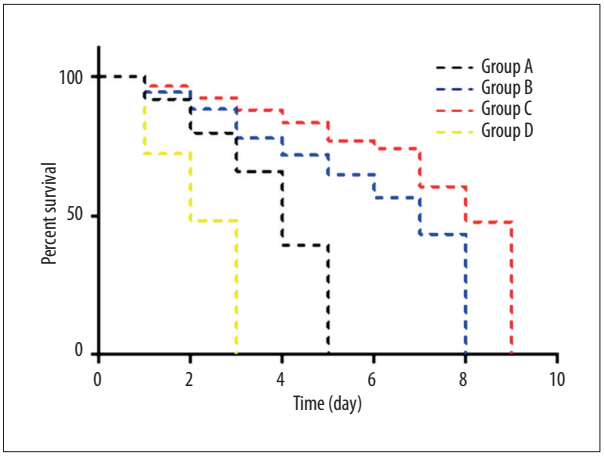

Figure 5. Survival of rats with sepsis after treatment with IL-15. Survival curves of the four groups show that group C survived longer than the other groups, followed by group B, then group A, and the untreated sepsis group had the shortest survival time.

methods. The increased survival of rats in group C, the cecal ligation model injected intraperitoneally with 1.5 μg of IL-15, indicated that the expression levels of IL-15 and IFN-γ, and the numbers of T cells and NK cells were correlated with the length of survival of the rats with sepsis (Figure 5).

Discussion

Recombinant interleukin-15 (IL-15) is a newly discovered drug that can be used in immunotherapy, but there have been few published studies on the use of recombinant IL-15 in the treatment of sepsis. Also, the effects of different doses of recombinant IL-15 on immune function and survival remain unknown. In this study, the effect of IL-15 on T cells, natural killer (NK) cells, and interferon-γ (IFN-γ) in a cecal ligation and puncture (CLP) rat model of sepsis were studied. The findings of the present study showed that in the rat model of sepsis, survival was prolonged by increasing the number of T cells and NK cells, and the levels of IFN-γ. Also, in the rat model of sepsis, treatment with recombinant rat IL-15 effectively increased peripheral levels of IL-15 and the percentage of peripheral T cells and NK cells, and IFN-γ levels. In the present study, treatment with recombinant IL-15 also prolonged the survival of rats in the sepsis model, and the higher the IL-15 levels, T cell and NK cell numbers, and IFN-γ levels, the longer the survival time. The findings of the study showed that the injection of recombinant IL-15 into rats with sepsis increased the number of T cells and NK cells, and the expression of IFN-γ. The doses of recombinant IL-15 doses ranging from 0.5 to 1.5 μg increased the percentage of peripheral T cells. The higher the dose, the higher the number of NK cells and the higher the expression level of IFN-γ. Also, the levels of these immune mediators were significantly higher at 48 h than at 24 h. However, the levels of all these immune mediators were significantly lower in the model rats with sepsis injected with saline when compared with the model rats with sepsis injected with recombinant IL-15, and lower in rats with sepsis injected with saline at 48 h than at 24 h.

From the findings of this study, treatment with recombinant IL-15 effectively increased the immune response in the rat model of sepsis, and this effect was associated with the inhibition of lymphocyte apoptosis. A previously published study by Inoue et al. [21] showed that IL-15 therapy increased the levels of antiapoptotic Bcl-2 while decreasing the levels of pro-apoptotic Bim and PUMA. Also, IL-15 increased both circulating IFN-γ, as well as the percentage of NK cells that produced IFN-γ, and improved the immune function in sepsis [21]. These findings support the findings of the present study, which suggest that IL-15 may improve immune function in rats with sepsis by preventing apoptosis and reversing immune dysfunction.

In a clinical study on the severity of sepsis, Chung et al. [22] reported that the levels of IL-7 and IL-15 in patients with severe lymphocytopenia in sepsis were reduced, which might be an important factor in the deterioration of patients with sepsis. In the present study, treatment with recombinant IL-15 increased the levels of circulating levels of IL-15 in rats with sepsis. Peripheral levels of IL-15 increased with increasing doses of recombinant IL-15, as did the survival times for rats with sepsis, indicating that circulating levels of IL-15 may be an important factor in the development of sepsis. In a study by Wang et al. [23], pretreatment of sepsis with recombinant human IFN-γ in a rat model effectively reduced T cell apoptosis, indicating that IFN-γ upregulates Bcl-2 expression to reduce T cell apoptosis. Therefore, targeted immunotherapy with IFN-γ may be an effective treatment of sepsis. In this study, analysis of the relationship between IFN-γ and sepsis showed that sepsis was not only affected by IFN-γ but also by other important immune cells. Although T cells and NK cells can produce IFN-γ, it remains unclear whether other IFN-γ-producing immune cells can have an equally important effect on sepsis. Therefore, further studies on T cells and NK cells are needed to obtain a definitive answer.

In a clinical study by Fang et al. [24] that investigated patients with sepsis in an intensive care unit, IL-10 and granulocyte colony-stimulating factor (G-CSF) levels and mortality in patients with active cancer were increased when compared with patients without active cancer. IL-10 is an anti-inflammatory cytokine that plays a crucial role in controlling inflammation and preventing enteritis [25], while G-CSF is also linked with the generation of IFN-γ [26]. Therefore, IL-10 and G-CSF should also be considered as potential treatments for sepsis.

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In the present study, rat recombinant IL-15 was used, rather than human recombinant IL-15. Although the responses of rat immune system are 80% similar to the human immune responses [27], it remains unknown whether human recombinant IL-15 can achieve the same results. Also, this study involved an animal model of sepsis, and controlled clinical studies are needed to further investigate the therapeutic role of recombinant IL-15 on recovery and survival in patients with sepsis.

Conclusions

In a rat model of clinical sepsis using cecal ligation and perforation (CLP), treatment with recombinant interleukin-15 (IL-15) prolonged the survival of rats by increasing circulating levels of IL-15 and interferon-γ (IFN-γ), and the numbers of peripheral T cells and natural killer (NK) cells. These preliminary findings in a rat model of sepsis may provide the impetus for further *in vivo* studies that add to knowledge regarding the control of the immune response triggered by sepsis.

Conflict of interest

None.

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