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Increased Survival After Cecal Ligation and Puncture in Mice Delivering Interleukin 12: The Role of T_H1 and T_H2 cells

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Abstract

Introduction: Severe injury is associated with depressed immune response. The purpose of this study was to analyze the role of T_H1 and T_H2 cells in the stimulated peripheral blood mononuclear cells and determine the effect of IL-12, a cytokine stimulating T_H1 cell proliferation, when administered to septic mice.

Methods: Male Balb/c mice underwent sham operation (group 1) or bacterial peritonitis (group 2) which was induced by cecal ligation and puncture and they were treated with IL-12 (group 3), or with IL-10 (group 4) or with both cytokines intraperitoneally (group 5). The T helper-1 (T_H1) and T helper-2 (T_H2) cells were analyzed following stimulation of peripheral blood mononuclear cells with poly-myristate-acetate (PMA) by measuring the intracytoplasmic expression of interleukin-4 (IL-4) and interferon-γ in $CD3^+$- lymphocytes with flow-cytometry. The survival rates of treated mice were compared with non-treated mice.

Results: The number of T_H1-cells in mice with peritonitis (group 2) was significantly lower than those in sham-operated mice (p=0.03). In contrast, the number of T_H2-cells was found to be higher in mice with peritonitis (p=0.001) compared to sham-operated. IL-12-administration restored the number of T_H1 and T_H2 cells to those of sham-operated ones. The survival rate of mice treated by IL-12 was found to be significantly improved compared to non-treated mice (p=0.002). However, IL-10 injection almost neutralized the restoring effect of IL-12 administration by improving the survival rate and the T_H1/T_H2 cell counts. Moreover, IL-10 administration alone resulted in lower survival than that of control and sham-operated group (p=0.002).

Conclusions: Changes in the T_H1 and T_H2 cells and/or cytokine balance in peritonitis in mice might induce a shift toward a T_H2 dominant phenotype. Therapies designed to increase the number of T_H1 cells such as IL-12 adminisration might be beneficial in the treatment of severe sepsis after peritonitis whereas IL-10 has a deleterious role in sepsis.

Keywords: T_H1 and T_H2 cells; Cytokine; Peritonitis; IL-10; Depressed immune response; IL-12; Septic mice, Cecal ligation and puncture; Intraabdominal sepsis.

Introduction

Cells and mediators of the innate immune system are required for induction of acquired immunity and for instructing the type of adaptive immune response [1,2]. The expression profile of cellular pattern includes both phagocytes and dentritic cells, which function as effectors of innate immunity and/or antigen presenting cells for the activation of T cells, respectively. Those cells

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responsible for initiating most adaptive immune responses in the T lymphocyte and injury induce alterations in T-cell function as they form a counter-reactive mechanism [3-5]. In patients and in animal models, serious injury was followed by loss of function of the T helper-1 (T_H1) lymphocyte subset with preservation of T helper-2 (T_H2) function, as indicated by cytokine production studied in vitro [4,6-9].

In animal models of injury, therapeutic regimens designed to increase T_H1 function have been associated with improved survival after a septic challenge [10-12]. Kavanagh and colleagues reported a mouse model of burn injury that early postinjury anti-IL-10 antibody treatment prevented the loss of T_H1 cell function, which is normally detected in injured mice [13]. On the other hand, due to the unopposed autocrine T_H1 response, anti-IFN-γ or anti-interleukin 12 (IL-12) therapy has markedly reduced the lethality induced by endotoxin in mice [14,15]. For this reason, the exact role of IL-12 and T_H1 cells in surgical trauma and sepsis are yet to be unveiled.

In the present study, the role of IL-12 administration along with IL-10 was investigated in abdominal septic model induced in mice by cecal ligation and puncture (CLP) peritonitis.

Material and Methods

Thirty outbred Balb/c male mice (weight range, 26 to 32 g) were used in all experiments. Animals were provided water and mouse food ad libitum. Ethical approval for the experimental animal study was obtained from the Istanbul University, Veterinary Faculty, Ethical Board. Mice undergoing sham or CLP were studied in groups of 6 or more. After induction of anesthesia with intraperitoneal pentobarbital (50 mg/g body weight**),** abdomens of all animals were shaved and opened in the midline. The cecum was delivered and ligated near its base (2/3 of its length) with a 4-0 silk ligature. The cecum was punctured twice with a 16-gauge needle and then was replaced in the abdomen, and the wound was closed with 3-0 atraumatic silk suture. Mice were resuscitated with 1.5 ml 0.9% saline intraperitoneally.

All mice were divided into 5 groups (6 mice in each group). The first group was the control group. No CLP was done in the second group, as the sham-operated group. The third and the fifth groups were treated with 0.5 µg recombinant mouse IL-12 (r-IL-12, Sigma Chemical Co., Steinberg, Germany) intraperitoneally as a first dose 30 minutes after the procedure in 0.25 mL saline beginning on the day of CLP and was continued for 10 days. The mice in the forth and fifth group, a single-dose 0.5 µg recombinant IL-10 (r-IL-10, Sigma Chemical co., Steinberg, Germany) was given after CLP in 0.25 mL saline. Mortality was monitored daily for a total of 50 days after CLP.

Induction and assessment of T_H1 and T_H2 Cells

Blood samples (50 µl) were collected 3 times from retroorbital sinus of mice at 12th, 24th and 36th hours after procedures. For intracellular cytokine staining, 3 whole blood samples (1×10^{6}/mL mononuclear cells) were stimulated with Poly-myristate-acetate (PMA) (50 ng/mL) plus ionomycin (500 ng/mL) for 4 hours at room temperature, then 5 µl monensin (2mmol) was added and incubated for 2 hours in dark and at room temperature. Cells then were stained with 5 µl fluorescein isothiocyanate (FITC)-mouse–anti-rat CD3 (0.5µmg/ml) (Pharmingen, San Diego, USA) and 5 µl FITC-mouse IgG1 (0.5 mg/ml) isotype-matched antibodies (Pharmingen, San Diego, USA) for 30 minutes at dark. Erythrocytes were eliminated using lysing solution (Becton-Dickonson, San Jose, USA) and BD *FACSFlow* solution (Becton-Dickonson, San Jose, USA) thoroughly. Cytofix/Cytoperm (Pharmingen, San Diego, USA) kit was used for fixation and permeabilization of the cells for immunofluorescent staining of intracytoplasmic cytokines. Two-hundred-fifty µl Cytofix/cytoperm solution was added to all wells and 200 µl cells (10^{6}/ml) were added each well and incubated for 30 min at 4 µC. Cells were again washed two times with 1X Perm/Wash buffer (Pharmingen, San Diego, USA), and with 250 µl Cytofix/Cytoperm solution(Pharmingen). The resuspended fixed/permeabilized cells were further stained with 5 µl phycoerythrin(PE)-mouse anti-rat IL-4 (0.2 mg/ml, Pharmingen, San Diego, USA) or 5 µl mouse anti-rat IFN-IL-4 (0.2 mg/ml, Pharmingen, San Diego, USA) or 5 µl PE-mouse IgG1 isotype-matched control antibodies (0.5 mg/ml, Pharmingen, San Diego, USA) for 30 minutes. Cells were washed two times with 1X Perm/Wash buffer resuspended with BD *FACSFlow* solution as final volume of a 500 µl sample and analyzed on a FACS Calibur (Becton Dickinson, San Jose, USA).

Statistical Analysis

Data are expressed as means ± standard deviation (SD). Student's t-test was used in comparative analyses of lymphocyte subsets analyses. A p value less than 0.05 was considered significant.

Results

The mean percentages of cytoplasmic IL-4-positive CD3+ T (i.e., T_H2 cells) lymphocytes were 3.4%, or 13.5%, or 17.3%, or 4.3% or 11.9 % in the sham-operated, or in the control CLP-group, or r-IL-10 administered, or r-IL-12 administered or r-IL-10 & r-IL-12 delivered mice at 36 hours after procedure, respectively (Table 1). CLP significantly increased T_H2 cells at 36 hours after CLP (p=0.0001), while r-IL-12 downregulated the increased T_H2 rates to the levels of the sham-operated group (Table 1).

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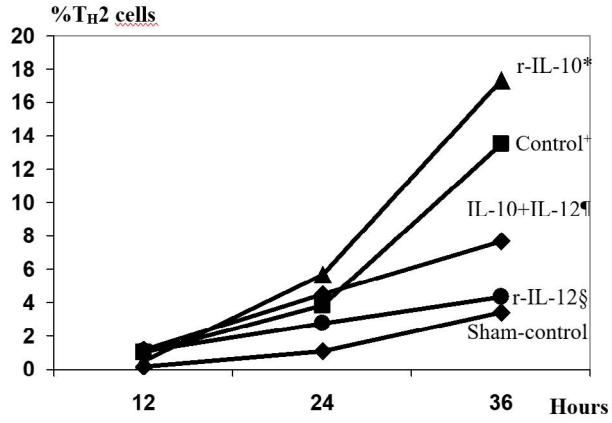
Table 1: The mean percentage rates (± Standard deviation) of IFN-gamma (IFN-G) and IL-4 rates and the survival time (day) in mice treated with IL-10 or IL-12 or IL-10&IL-12 in a septic model induced by cecal ligation and puncture.

	IL-4	IFN-G	IFN-G/IL-4
Sham-group	3.42±0.87	4.93±1.76	1.43±0,23
CLP-group	13.52±2.97	11.81±9.31	0.84±0,63
IL-10	17.31±15.31	4.31±1.37	0.32±0,11
IL12	4.35±2.18	14.49±5.51	3.65±1,28
IL-10/IL-12	11.85±3.16	7.78±3.48	0.71±0,41

r-IL-10 prominently increased the T_H2 cell rates (Figure 1; p=0.0001). However, r-IL-10 had no significant effect on T_H2 cells when administered along with r-IL-12 (p= 0.59). There was a statistically significant increase of the T_H2 cell rates in the control-CLP-group compared to the sham-operated mice at 36 hours (p=0.03).

Furthermore, r-IL-10 administration decreased T_H1 cells to 4.31% which was nearly the same levels of the sham group (4.93%) at 36 hours after the procedure, even though this difference did not reach the statistical significance (p=0.11). r-IL-12 treatment slightly increased the T_H1 numbers at 36 hours after application (p=0.56), even though this difference did not reach the statistical significance. Similarly, injection of both r-IL-10 and r-IL-12 did not result in an increase in T_H1 levels (p=0.37) (Figure 2).



*: p=0.001 (vs control group)

+: p=0.002 (vs control group)

¶: p>0.05 (vs control group), p=0.03 vs sham group.

Figure 1: Cecal ligation and puncture (CLP) statistically increased T_H2 cells at 24 and 36 hours after CLP. However, r-IL-12 decreased the number of T_H2 cells to that of sham group.

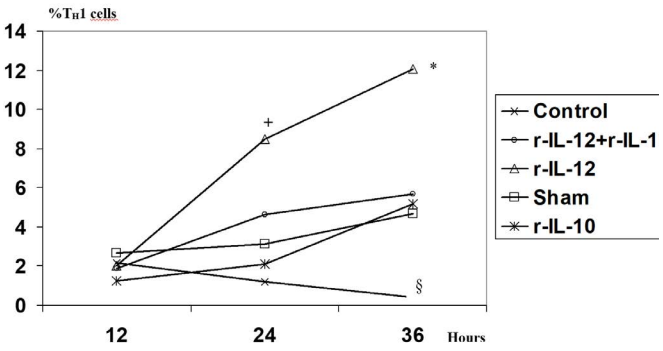


Figure 2: Cecal ligation and puncture (CLP) decreased T_H1 cells at 24 and 36 hours after CLP. r-IL-10. r-IL-12 prominently induced T_H1 proliferation at 24 hours (+: IL-12 vs control, 24 h, p=0.01) and 36 hours (*: IL-12 vs control, 36 h, p=0.002) after CLP. On the contrary, r-IL-10 reduced the T_H1 cells at 36 hours after CLP(§: IL-10 vs control, 36 h, p=0.01).

No deaths occurred in sham-operated mice during first month of experiment. r-IL-10 statistically significantly decreased the survival of mice (p=0.001), while r-IL-12 administration significantly improved survival of mice (p=0.0001). r-IL-10 decreased the therapeutic efficacy of IL-12 when added to IL-12 injections, however the combination group received both IL10&IL-12 significantly survived longer than the control-CLP-group (p=0.003) (Figure 3).

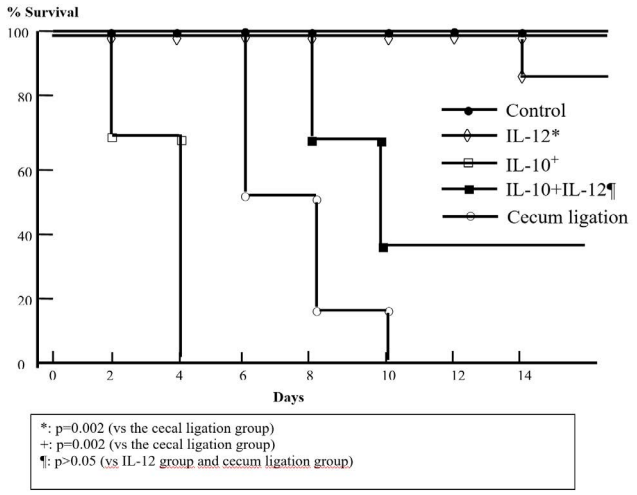


Figure 3: The survival rates of severe peritonitis mice treated with r-IL-12, IL-10 or both. The survival was improved by r-IL-12, whereas it was worsened by r-IL-10. r-IL-10 neutralized the effect of r-IL-12.

Discussion

Bacterial infection and/or visceral trauma leads to activation of cytokine network, which comprises proinflammatory cytokines, anti-inflammatory cytokines, and soluble inhibitors of proinflammatory cytokines. There is still

Kiran B, et al., Arch Clin Biomed Res 2025
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debate whether proinflammatory cytokine activity is linked to an adverse outcome in infectious disease. Clinical trials with anti-inflammatory strategies in patients with severe bacterial infections are based primarily on animal studies in which bacteria or bacterial products were administered systemically in the absence of a localized infectious source [5,7,-9,11,14]. Activation of inflammatory pathways, including the cytokine network, is considered to play a major role in pathogenesis of sepsis. The particular type of immune response is determined by the differentiation of naïve helper T (T_H0) cells into T_H1 and T_H2 cells, which can be induced to express the T_H1 phenotype by exposure to the cytokine IL-12, whereas exposure to IL-4 induces T_H2 phenotype [4,6]. It has been reported that, in humans and experimental animals, serious injury is associated with a loss of function and of cytokine production by the T_H1 subset of lymphocytes, whereas T_H2 function and cytokine production are apparently maintained or increased [4,6-8,10, 11, 17]. Because IL-12 is known to be the principal agent that induces naïve T-helper cells to become the T_H1 phenotype [12]. The diminished capacity to produce IL-12 by the usual cellular sources of this cytokine, even when maximally stimulated by bacterial lipopolysaccharides may explain at least in part the apparent inability to maintain T_H1 function and cytokine production [3,4,7,8].

Baker et al. [18] first described the CLP model in mice based on rat model developed by Wichterman and colleagues [19]. In contrast to models based on intravascular or intraperitoneal administration of endotoxin-bacteria, CLP represents a peritonitis model with clinical features of the infection comparable with those of peritonitis in patients. It was demonstrated that higher percentages of lymphocyte-associated TNF-α, IL-10, IL-6 and IL-12 and monocyte-associated TNF-α, IL-10, and IL-12 in septic patients with a better prognosis suggesting that both T_H1 and T_H2-cell responses were necessary for the survival of the septic patients [20]. In a recent report, it was concluded that, sepsis immunodeficiency is associated with loss of delayed type of hypersensitivity (DTH), failure to eliminate primary infections, and propensity to acquire secondary infections [21].

In this study, we showed that, peritonitis might result in a shift in the cytokine production toward T_H2 phenotype according to intracytoplasmic cytokine assessments of the lymphocytes. Furthermore, intraperitoneal IL-12 injection provided an improved survival in the peritonitis model of mice. In order to show the role of IL-10 in the development of deleterious effects of peritonitis, we demonstrated that IL-10 injection reversed the survival-improving effect of IL-12. These findings suggest that severe peritonitis is accompanied by a shift to predominance in T_H2 cells, and a shift toward to T_H1 cells is important for the recovery from this condition. Ono and colleagues also demonstrated the beneficial effect of IL-12 in cecal ligation and puncture; however, they analyzed the cytokine contents of the serum samples and supernatants of liver mononuclear cells [22]. Although, the major producers of IFN- γ was known to be lymphocytes namely T lymphocytes, NK cells and/or monocytes in the blood and connective tissue and monocytes in liver mononuclear cell culture might contribute IFN- γ and IL-10 levels. Short plasma half-life of circulating cytokines, soluble cytokine receptors or inhibitors, and peripheral blood cells such as erythrocytes or leukocytes trapping excessive exogenous cytokines via their receptors can cause a reduction of these individual cytokines, resulting in misleading results. Findings indicate that leukocyte intracytoplasmic cytokine levels should be discussed separately from their corresponding serum levels. A powerful diagnostic tool has become available to discriminate a shift of functionality in T-cell subsets via their individual cytokine profiles by performing flow cytometric analysis [23]. Intracellular cytokine analysis has been accepted as the state-of-the-art analysis for T_H1/T_H2 subsets [24]. In addition, in our study, no sacrification of mice was necessary in order to obtain liver mononuclear cells. Using peripheral blood mononuclear cells for the analysis, it is easily repeatable and non-invasive. We also were able to monitor the number of T_H1 and T_H2 cells rather than its secreted cytokines at different time-points after CLP. However, we stimulated the isolated mononuclear cells and the degree of representation of sepsis immunity should be justified. Nonetheless, immune reaction cascade was documented to involve systemic immunity in sepsis [3-11,13-15]. For this reason, it is reasonable to suggest that, the analysis for T_H1/T_H2 subsets is theoretically more informative and can give more insight into the *modus operandi* of systemic immune response to sepsis. Our data suggested that in the severe sepsis or in the late period of sepsis, the number of T_H1 cells were markedly decreased. However, after IL-12 administration, the number of T_H1 cells was increased at 24, 36 hours after sepsis induction and survival rates were increased. In conclusion, in severe sepsis the neutralization of T_H1 cytokines could increase mortality and boost counter-effective T_H2 cell number and immune modulation with such immunostimulatory reagent as IL-12 would be recommended. Although Docke and associates [25] demonstrated the beneficial effect of T_H1 induction by IL-12, Steinhauser et al. [26] demonstrated IL-12 increased sepsis-induced lethality. Thus, no consensus existed on the effect of IL-12 administration in sepsis. The role of IL 10 after the onset of sepsis is less clear showing diametrically opposite effects of anti-IL-10 therapy in animal models of bacterial infection [27-29]. However, different sepsis models were utilized in these investigations. Nevertheless in our study, IL-10 worsened the prognosis of mice undergoing CLP.

Therapies designed to increase the number of T_H1 cells such as IL-12 adminisration might be beneficial in the

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treatment of severe sepsis after peritonitis whereas IL-10 has a deleterious role in sepsis. Since the benefit of IL-12 therapy is supported by the present experimental study, future studies should be focused on the therapeutic effect of IL-12 in patients with severe sepsis.

Conflict of Interest: None of the authors have conflict of interest.

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Manuscript Review-Editing: Zeybek Ü, Turna A, Durmaz H, Cabioglu N, Deniz G.

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