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ORIGINAL ARTICLE

Photobiomodulation modulates the resolution of inflammation during acute lung injury induced by sepsis

Marlon da-Palma-Cruz[1] · Rodrigo Fernando da Silva[1] · Dhuane Monteiro[1] · Hassan Mohamed Mohamed Abdel Rehim[1] · Caren Cristina Grabulosa[1] · Ana Paula Ligeiro de Oliveira[1] · Adriana Lino-dos-Santos-Franco[1]

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Abstract

Sepsis is a big health problem and one of the most common causes of acute lung injury (ALI) leading to high mortality. Pro-resolving mediators play an important role in abrogating the inflammation and promoting tissue homeostasis restoration. ALI treatment is still a clinical health problem, so new therapies are needed. Here, we evaluated the effect of photobiomodulation treatment on the resolution process of ALI induced by lipopolysaccharide (LPS). Male Balb/c mice were submitted to LPS (ip) or vehicle and irradiated or not with light emitting diode (LED) 2 and 6 h after LPS or vehicle injection, and the parameters were investigated 3 and 7 days after the injections. Our results showed that after 3 days of LED treatment the blood and bronchoalveolar lavage (BAL) cells as well as interleukins (IL) including IL-6 and IL-17 were reduced. No differences were observed in the bone marrow cells, tracheal reactivity, and lipoxin A4 and resolvin E2. Indeed, after 7 days of LED treatment the bone marrow cells, lymphocytes, and lipoxin A4 were increased, while IL-6, IL-17, and IL-10 were decreased. No differences were observed in the blood cells and tracheal reactivity. Thus, our results showed that LED treatment attenuated ALI induced by sepsis by modulating the cell mobilization from their reserve compartments. In addition, we also showed later effects of the LED up to 7 days after the treatment. This study proposes photobiomodulation as therapeutic adjuvant to treat ALI.

Keywords Acute lung injury · Photobiomodulation · Lipoxins · Resolvins · Cytokines · Tracheal responsiveness

Introduction

Sepsis is a big health problem often caused by Gram-negative bacteria (35% of cases) and one of the. most, common, causes of acute lung injury (ALI), mostly in hospital settings. However, it can, be also associated with a variety of non-infectious events such, as multiple trauma, surgeries, and burns [1]. Sepsis is one of the main causes of hospital mortality, overcoming myocardial, infarction and cancer [2].Neutrophils are pivotal cells in the ALI, playing a relevant role through release of several inflammatory, mediators including cytokines, elastase, and oxygen reactive species [3–5]. Still, neutrophils are considered as biomarker of severity of disease [6, 7]. Therefore, some studies have proposed the induction of neutrophil apoptosis as a strategy of treatment [3, 4].

During ALI, several mediators have been identified in inflammatory site and play an important role in the resolution of the inflammatory response [8–10]. Such mediators are potent regulators of inflammatory cell infiltrates, cytokine and chemokine production, and clearance of apoptotic neutrophils, thus promoting tissue homeostasis restoration. Therefore, this process seems to be crucial for ALI. Resolution of inflammation is a biochemically, active process, regulated, at least in part, by mediators derived from endogenous polyunsaturated fatty acids (PUFAs), which act as potent local resolution agonists [11, 12], including lipoxins, resolvins, and maresines [13]. Lipoxins as well as resolvins are important against oxidative injury and contribute to the reestablishment of vascular permeability, thereby reducing edema [14–16]. Recent studies have shown that resolvin D1 exerts anti-oxidant, anti-inflammatory, and pro-resolution effects in animal models of ALI [17–19].

The restoration of normal lung, function is complicated and based :on the reduction of edema, neutrophil clearance, and

✉ Adriana Lino-dos-Santos-Franco
alsantosfranco@gmail.com

[1] Post Graduate Program in Biophotonics Applied to Health Sciences, University Nove de Julho (UNINOVE), Rua Vergueiro, 239/245, São Paulo, SP CEP 01504-000, Brazil

alveolar barrier repair among others. In this context, the treatment, of ALI is a clinical problem, since the available therapies are inefficient [20–23]. Additional approaches have been integrated into the therapy, such as mechanical ventilations with a low volume, prone position, and an extracorporeal membrane oxygenation. Nevertheless, these treatments require high costs and they are not sufficiently effective. Thus, new treatments are needed.

Photobiomodulation such as light-emitting diode (LED) is based on the effects of light on damage tissues, and has been pointed as promisor tool for the treatment, of lung diseases including ALI [24–29]. Recently, we have shown that LED treatment reduced the influx of neutrophils induced by LPS; decreased the levels of IL-1β, TNF-α, IL-17A; and increased IFN-gamma levels in the bronchoalveolar lavage fluid (BAL). In addition, LED treatment, increased IL-10 and IFN-gamma mRNA levels, partially reduced the high, oxidative burst, and increased the expression of annexin V contributing, to the lower migration of neutrophils. No differences were observed in the activation of NF-kappa B expression, TLR4, edema, and mucus production [30]. Thus, our data showed, for the first time, the beneficial effect of LED treatment on sepsis-induced ALI.

Despite of the important role of resolution process in ALI and based on the previous studies, we have hypothesized that the LED treatment could modulate the resolution of inflammatory process favoring the reestablishment of lung homeostasis. Using an experimental model of sepsis induced by lipopolysaccharide (LPS), we performed a timeline study focusing on leukocyte mobilization, secretion of cytokines, lipoxins, resolvins, and tracheal responsiveness.

Materials and methods

Animals

Male mice, Balb/c (~20 g, 60 days) obtained from: the University Nove de Julho were maintained in a light- and temperature-controlled room; (12/12-h light-dark cycle, 21 ± 2 °C), with free access to food and water. The experiments were approved by the Animal Care Committee University Nove de Julho (CoEP-UNINOVE; AN005/2017).

Acute lung injury induced by lipopolysaccharide

According to earlier studies [30], mice were submitted to injection of lipopolysaccharide (LPS; *Samonella abortus equi*, 5 mg/kg, ip) or vehicle (saline) to induction of ALI. It is well established that LPS is a good and widely model employed to induce ALI. It produces the main characteristics of disease including elevate neutrophils influx, diffuse alveolar damage, loss of alveolar epithelium, edema, and impaired gas exchange. Three and 7 days after the LPS or vehicle injection the animals were euthanized by sectioning the abdominal aorta under with anesthesia (ketamine 100 mg/kg and xylasine 10 mg/kg, ip).

Photobiomodulation therapy

Mice were irradiated 2 and 6 h after LPS or vehicle injection in the respiratory tract (lungs and trachea) by direct contact with skin according to Costa et al. [30]. The parameters follow above:

Wavelength: 660 nm (full width at half maximum 20 nm)
Potency: 100 mW
Radiant exposure: 5 J/cm^2
Irradiance: 33.3 mW/cm^2
Area: 2.8 cm^2
Total energy: 15 J
Time of irradiation: 150 s.

Experimental groups

Mice were divided into five experimental groups:

1) Basal group: non-manipulated mice
2) LPS3 group: mice submitted to LPS, treated with placebo (light off), and euthanized 3 days after the LPS injection
3) LPS7 group: mice submitted to LPS, treated with placebo (light off), and euthanized 7 days after the LPS injection
4) LPS3 + LED group: mice submitted to LPS, treated with LED, and euthanized 3 days after the LPS injection
5) LPS7 + LED group: mice submitted to LPS, treated with LED, and euthanized 7 days after the LPS injection.

We also evaluated group of mice submitted to vehicle of LPS and treated with LED using the same protocol above. However, no differences were observed in relation to basal group. So, we showed basal group as control. In all experimental set, we used six animals per group.

Experimental design

Cell count in the blood, bone marrow, and lung

Considering, the important role of leukocytes in the development of ALI, the number of leukocytes was evaluated in different ,storage compartments. Global leukocyte count was evaluated thought Neubauer chamber (Turk's solution), while differential count was quantified on blood smears stained.

The differential cells obtained from bronchoalveolar lavage (BAL) were evaluated by cytometry flux as described earlier [30].

Quantification of cytokines and pro-resolving mediators in the bronchoalveolar lavage

Cytokines were investigated in the BAL fluid. The results were expressed as pg/ml. IL-17A, IL-6, and IL-10 were quantified using ELISA Kits purchased from Biolegend (San Diego, USA). Resolvin D1, E1, and lipoxin A4 were quantified using ELISA Kits purchased from MyBioSource (Vancouver, Canada). Determinations were made, in duplicate for every, sample using standard curves according to the manufacturer's specifications.

Tracheal responsiveness to methacholine

In order to investigate the effects of LED on the tracheal contractile response, isometric force was quantified, in tracheal rings mounted, in a 15-ml organ bath by means of two steel, hooks according to [31]. Force contraction was recorded using a force displacement transducer and a chart recorder (Powerlab®, Labchart, AD Instruments). Tracheal rings were suspended in organ bath filled with continuously aerated (95% O_2 and 5% CO_2) Krebs-Hanseleit (KH) solution at 37 °C. After 40 min, the tracheal tension that was adjusted to 0.5 g e was added methacholine (MCh; 10^{-3} M) in order to obtain maximum contractile response.

Statistical analyses

Data were expressed as the means ± SEM, and comparisons among the experimental groups were analyzed by one-way ANOVA followed by the Student's Newman-Keuls test for multiple comparisons using the GraphPad software v.5. *P* values less than 0.05 were considered statistically significant.

Results

Effects of LED treatment on the resolution of cellular recruitment in the blood and in the bone marrow

Leukocyte mobilization is an initial hallmark for the development of acute injury. Our data showed that LED treatment in the LPS3 group reduced significantly the number of total cells, neutrophils, lymphocytes, and monocytes in the blood, while in the LPS7 group no differences were observed when compared to non-treated animals (Fig. 1, a, c). Moreover, we showed elevated number of total cells and neutrophils in LPS3 group when compared to the basal group.

In Fig. 1c, d, we can observe that both LPS3 and LPS7 groups had a decrease in the bone marrow cells when compared to the B group. The LED treatment only reversed the reduced number in LPS7 group. No effects of LED treatment were observed in LPS3 group.

Effects of LED treatment on the resolution of cellular recruitment in the bronchoalveolar lavage

Figure 2a shows that LED treatment in the LPS3 group did not alter the elevated number of total cell into the BAL when compared to non-treated group. On the other hand, the LED treatment in the LPS7 group increased the number of total cells in the BAL when compared to non-treated group (Fig. 2b). We also showed that LPS3 group showed elevated number of cells in relation to B group, while LPS7 group did not present differences between B group (Fig. 2a, b).

In Fig. 2c, we can observe that LED treatment in the LPS3 group reduced the number of neutrophils, lymphocytes, and macrophages, while in the LPS7 group reduced only the number of lymphocytes when compared to non-treated mice.

Effects of LED treatment on the cytokines released in the bronchoalveolar lavage fluid

Figure 3a–c shows that LED treatment in the LPS3 group reduced the level of IL-6 and IL-17 and did not alter IL-10 in the BAL fluid when compared to non-treated group. Elevated level of IL-17, but not IL-6 and IL-10, was found in LPS3 group in relation to B group. On the other hand, LED treatment in the LPS7 group decreased the level of IL-6, IL-17, and IL-10 in BAL fluid when compared to non-treated group (Fig. 3d–f). We also showed elevated level of IL-6 in the LPS7 group in relation to B group.

Effects of LED treatment on the release of lipoxin A4 and resolvin E2 in the bronchoalveolar lavage fluid

Figure 4a, b shows that no differences in the lipoxin A4 as well as resolving E2 were observed among the groups of study. Elevated level of lipoxin A4 was found in LPS7 group after LED treatment when compared to non-treated group. Indeed, no differences in the resolving E2 were observed among the groups of study (Fig. 4c, d).

Effects of LED treatment on the maximum smooth muscle contractile response to cholinergic stimulus

As can be observed in Fig. 5a, b, LED treatment did not reverse the increased contractile response in both LPS3 and LPS7 groups. Indeed, we showed increased tracheal responsiveness in LPS3 and LPS7 groups in relation to B group.

Discussion

ALI is one of the most devastating complications of sepsis and septic shock [32]. Lesion in the alveolar epithelium plays a critical role in the pathogenesis of ALI, which is

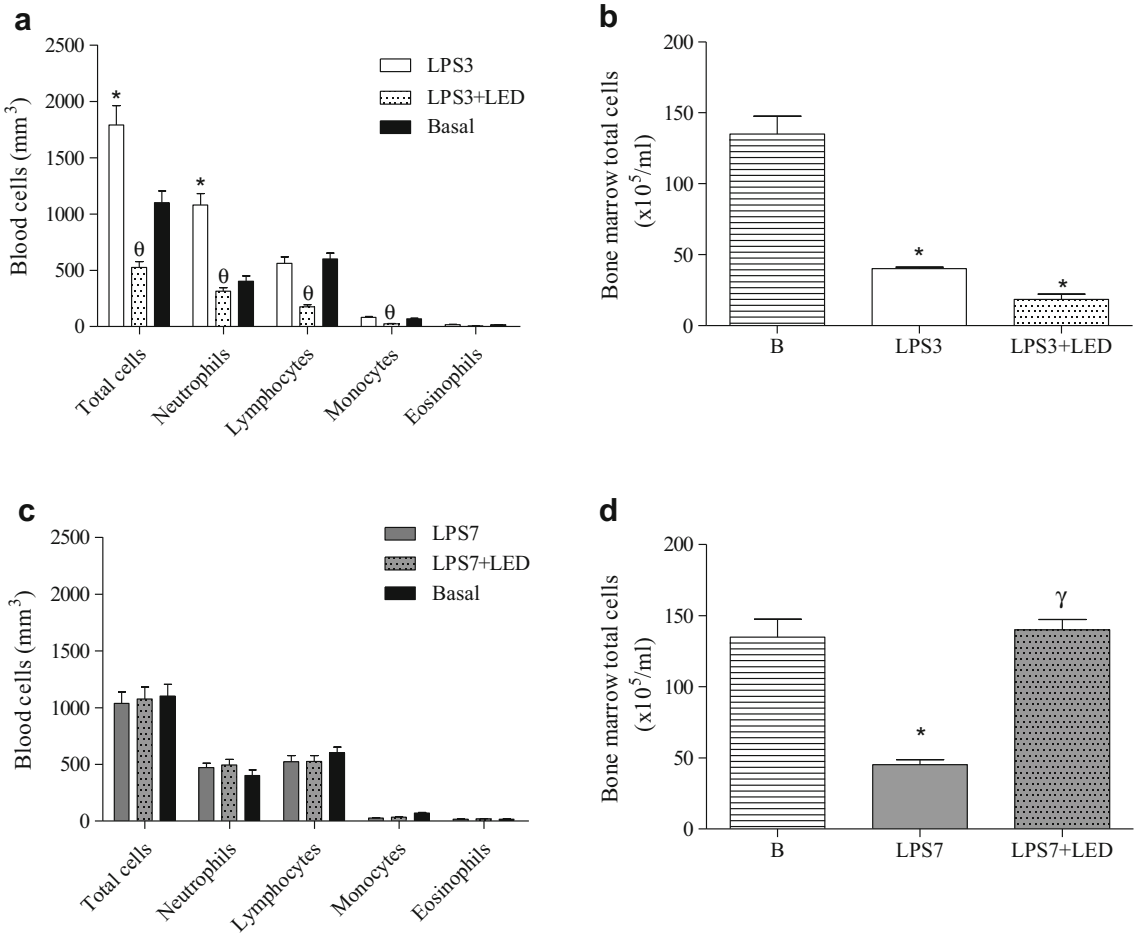

Fig. 1 Effects of photobiomodulation in the cell mobilization from blood and bone marrow after acute lung injury. Groups of mice with acute lung injury induced by LPS were treated or not with LED. In parallel, non-manipulated animals were used as control (basal group). After 3 and 7 days of LPS injection, blood leukocytes as well as bone marrow cells were quantified. Data represent the mean ± 6 animals per group. Data mean ± SEM of 6 animals per group. $^{*}P < 0.05$ in relation to B group; $^{\theta}P < 0.05$ in relation to LPS3 group; $^{\gamma}P < 0.05$ in relation to LPS7 group

characterized by loss of junctions and alveolar barrier function leading to intense infiltration of innate immune cells, especially neutrophils. These cells contribute to alveolar injury through the secretion of oxidants and proteases in the alveolar epithelium and endothelium, leading to a higher surface tension, of the, alveoli and1 a greater propensity2 to collapse [33]. Considering the complications as well as high mortality of sepsis, new therapies are needed to be investigated. Here, we advance in our studies showing promising effects of photobiomodulation to treat ALI.

Recently, our group showed that LED treatment reversed the acute lung injury induced by sepsis by reducing not only the number of neutrophils but also their activation. These effects were modulated by the decreased levels of IL-1β, IL-17A, and TNF-α, concomitantly to elevated levels of IFN-γ and IL-10 expressions. Reduced production of reactive oxygen species (ROS) was also observed [30]. These data were promisor and here we decided to investigate the resolution process during ALI and its modulation by LED treatment. In earlier study, we focused the role of LED in the acute phase of ALI; for this purpose, the parameters were analyzed 24 h after the LPS injection. On the other hand, in the present study we aimed to investigate if LED can modulate the resolution process of inflammation increasing the release of resolution mediators such as resolvins and lipoxins. In addition, the approach used here allows us to evaluate the later repercussions of LED, since the parameters were analyzed 3 and 7 days after the LPS injection.

In order to evaluate the interference of LED on the resolution response of inflammation, the parameters were evaluated 3 and 7 days after the last LPS injection. This protocol aimed to evaluate if the treatment with LED during the development of the inflammation could interfere in the resolution process, eventually causing its facilitation or acceleration.

In an attempt to understand the dynamics of cell migration during the inflammatory process, we investigated the number of cells in the peripheral blood as well as in the bone marrow. Our data showed that monocytes were increased in the blood after 3 or 7 days of LPS induction, and neutrophils were increased only after 3 days returning to basal values after 7 days

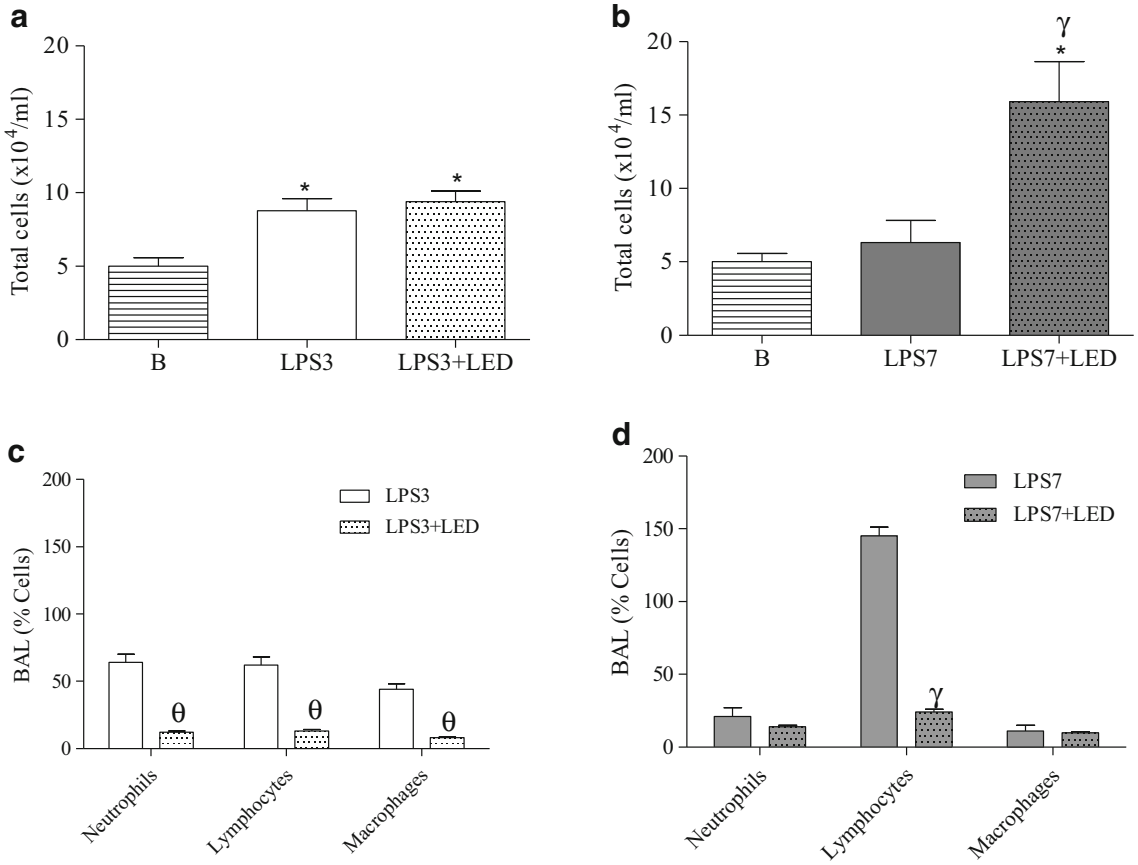

Fig. 2 Effects of photobiomodulation in the migrated cells into BAL after acute lung injury. Groups of mice with acute lung injury induced by LPS were treated or not with LED. In parallel, non-manipulated animals were used as control (basal group). After 3 and 7 days of LPS injection, the leukocytes present in the BAL were quantified. Data represent the mean ± 6 animals per group. Data mean ± SEM of 6 animals per group. $^{*}P < 0.05$ in relation to B group; $^{\theta}P < 0.05$ in relation to LPS3 group; $^{\gamma}P < 0.05$ in relation to LPS7 group

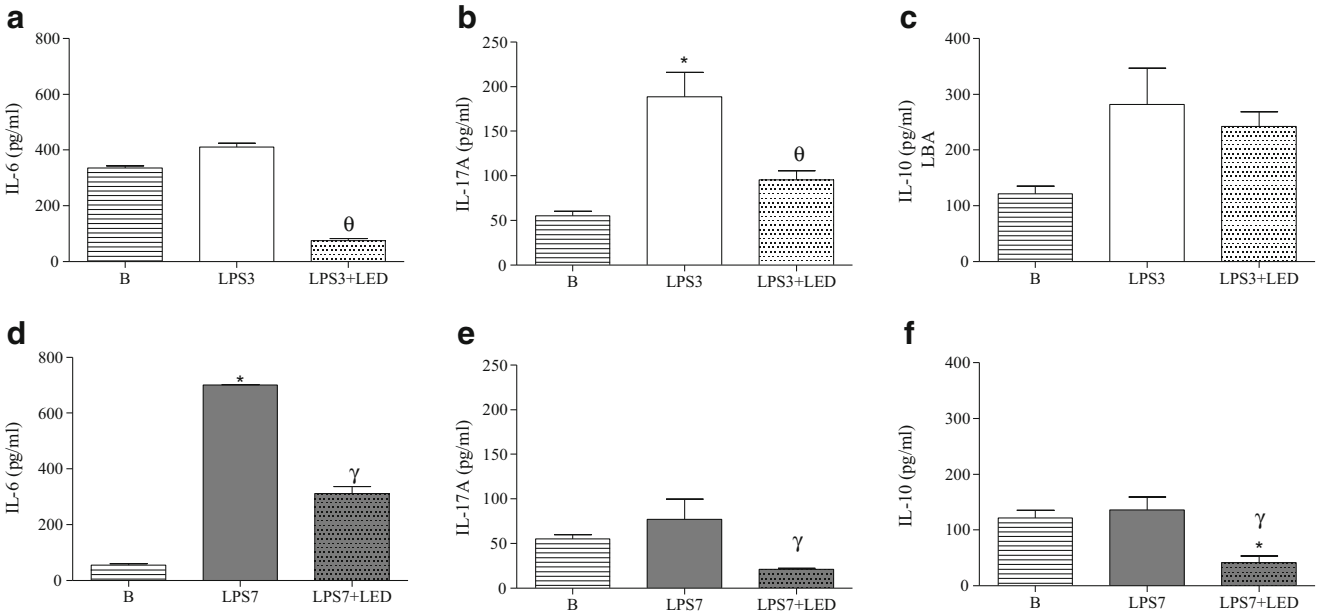

Fig. 3 Effects of photobiomodulation in the cytokines released in the BAL fluid after acute lung injury. Groups of mice with acute lung injury induced by LPS were treated or not with LED. In parallel, non-manipulated animals were used as control (basal group). After 3 and 7 days of LPS injection, the cytokines were quantified. Data represent the mean ± 6 animals per group. Data mean ± SEM of 6 animals per group. $^{*}P < 0.05$ in relation to B group; $^{\theta}P < 0.05$ in relation to LPS3 group; $^{\gamma}P < 0.05$ in relation to LPS7 group

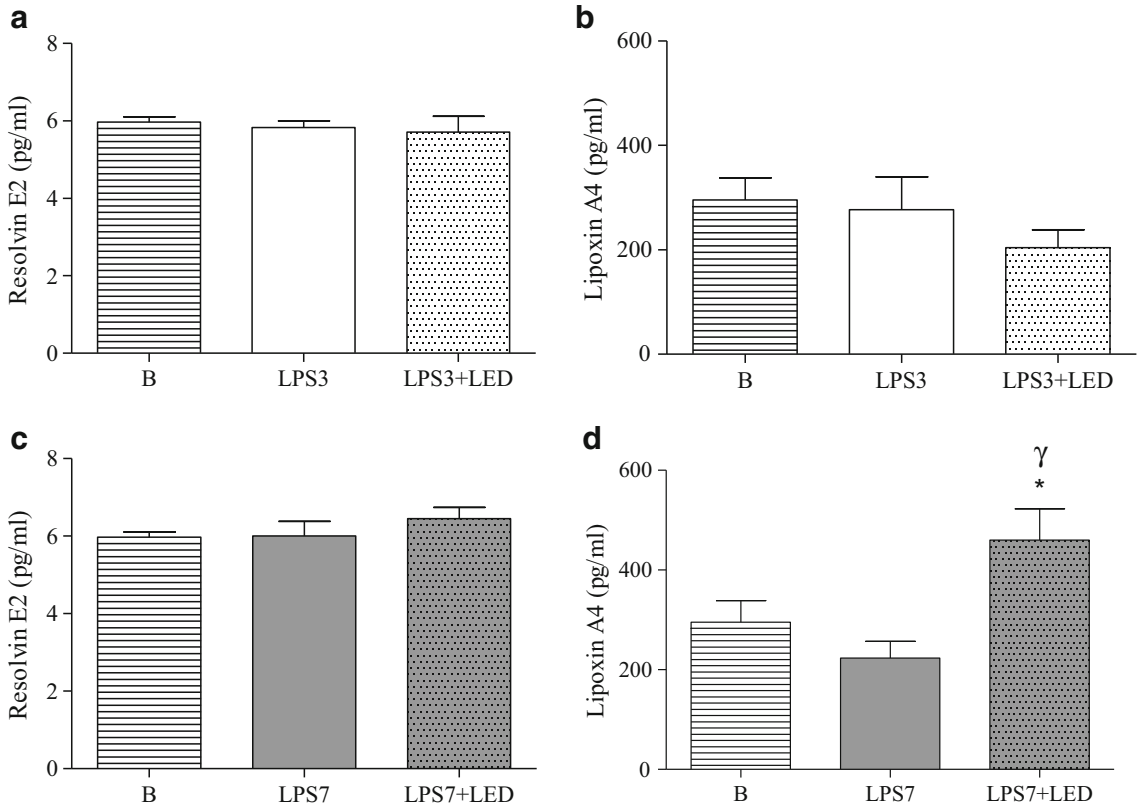

Fig. 4 Effects of photobiomodulation in the levels of resolving and lipoxin released in the BAL fluid after acute lung injury. Groups of mice with acute lung injury induced by LPS were treated or not with LED. In parallel, non-manipulated animals were used as control (basal group). After 3 and 7 days of LPS injection, the level of resolving E2 and lipoxin A4 were quantified. Data represent the mean ± 6 animals per group. Data mean ± SEM of 6 animals per group. $^{*}P < 0.05$ in relation to B group; $^{\gamma}P < 0.05$ in relation to LPS7 group

to sepsis-LPS induction. LED treatment reduced neutrophils, monocytes, and lymphocytes in the blood only in the LPS3 group without altering the number of cells in the LPS7 group. Despite of the LED treatment were performed directly in the respiratory tract, systemic effects were observed impacting in the modulation of blood cells. Indeed, late effects on the dynamic of blood migration were noted, when we consider that the LED irradiation was performed 2 and 6 h after the LPS injection and the parameters were investigated 3 days after. During the inflammation, mechanisms are triggered to blunt the inflammatory cell recruitment in order to restore lung homeostasis. This process is controlled by several mediators and characterizes the resolution process.

Still, we also investigated the cellularity in the bone marrow in order to understand the cell mobilization from the reserve compartment. Our data showed a marked reduction in the total number of cells present in the bone marrow in both groups LPS3 and LPS7. This reduction showed that the homeostasis was not established after 7 days, although many parameters had returned to basal values. On the other hand, LED treatment reversed the reduced number of cells in the bone marrow in LPS7 group, but did not alter in LPS3 group. Considering this difference in the bone marrow cell count between LPS3 and LPS7 after the LED treatment, we might assume that the photobiomodulation here seems to contribute with resolution process during inflammation.

This hypothesis was reinforced by the effects of LED in the lung cell migration. LED treatment reduced neutrophils, macrophages, and lymphocytes in the LPS3 group. In contrast, when the parameters were evaluated 7 days after the induction, we observed increased influx of cells into the alveolar space after LED treatment. This result was surprising, considering that after 7 days of LPS induction, non-treated animals presented the number of cells in the BAL similar to basal group. Thus, our data showed that during 7 days the body itself was able to restore its lung homeostasis. But, despite of the LED treatment caused an increase in the total cells in the BAL of LPS7 group, such result, at the first time, seems to be contradictory. However, we must consider that LED elevated only the number of lymphocytes, and eventually, these cells could have an anti-inflammatory phenotype such as T regulatory, thus contributing to resolution process of inflammation. This is a hypothesis analyzing all of results together, but will be tested in the future.

Recognizing that1 the cell migration2 process is controlled by several factors including pro-inflammatory and anti-inflammatory cytokines, we sequentially investigated the release of IL-6, IL-17, and IL-10 in BAL fluid. Our data

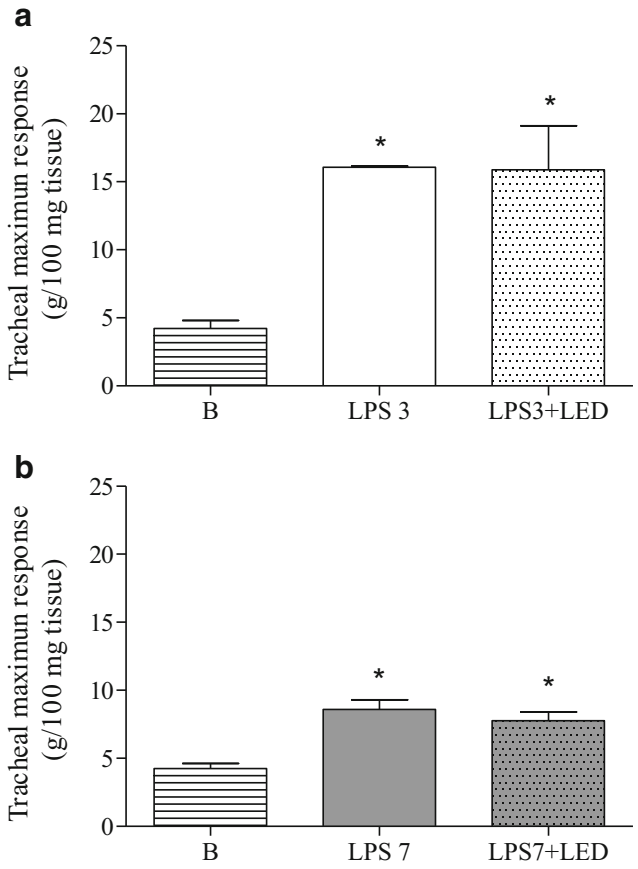

Fig. 5 Effects of photobiomodulation in the tracheal maximum contractile response after acute lung injury. Groups of mice with acute lung injury induced by LPS were treated or not with LED. In parallel, non-manipulated animals were used as control (basal group). After 3 and 7 days of LPS injection, the tracheal responsiveness to methacholine was evaluated. Data represent the mean ± 6 animals per group. Data mean ± SEM of 6 animals per group. *$P < 0.05$ in relation to B group

showed elevated level of IL-6 in the LPS7 group, but no differences were observed in LPS3 group. Regarding the LED treatment, a significant reduction in IL-6 was observed in both LPS3 and LPS7 groups. This result contributes to facilitate the resolution process, since IL-6 is considered a pleiotropic cytokine, playing a central role in the pathophysiology of ALI. It is a biomarker1 of disease severity and is 1associated with poor1 prognosis and risk of death [34–36]. It also plays a central role in host defense against environmental stress, such as infection and injury, and may increase more than 100,000 times1 during the early1 stages of inflammation [37]. It also emphasized that neutrophils are key cells and large producers of IL-6 in this model.

Interleukin 17A (IL-17A) is a cytokine 1produced primarily 1by activated TCD4 cells, which 1stimulate the secretion of IL-6 and IL-8 by human 1fibroblasts, and plays an important role in2 protecting the body2 against bacteria and4 fungi, due to its potent ability ’to recruit neutrophils [38]. In addition to the ability to recruit neutrophils, IL-17A increases the permeability of the alveolar epithelium, favoring plasma extravasation into the alveolar 4spaces, which, together with the elimination7 of damaged alveolar fluid, leads1 to edema alveolar [39]. Furthermore, neutrophils are also producers of IL-17 [40]. Our data showed that 3 days, but not 7 days after LPS injection, we found that elevated amounts of IL-17 and LED treatment reduced this cytokine. These data may reflect the lower lung inflammation after LED treatment.

An important anti-inflammatory cytokine, IL-10, was also evaluated and no differences were observed after LPS injection. On the other hand, LED treatment caused a reduction in the IL-10 level in LPS7 group. This data was intriguing and needs to be investigated in the future.

Resolvin E2 as well as lipoxin A4 are a class of endogenous lipid mediators that are generated during the resolution phases of an acute inflammation. Both mediators inhibit the progression of acute inflammation and induce the phases of resolution in various processes, such as4 in efferocytosis and in tissue 1repairs [41]. Here, we showed elevated level of lipoxin A4 in LPS7 group after LED treatment. Thus, this data can reflect the elevated number of lymphocytes in LPS7 group and strengthens our hypothesis about the anti-inflammatory phenotype of lymphocytes. Finally, we showed that LED treatment did not alter the tracheal responsiveness to methacholine despite of it reduced the lung inflammation. This data showed that LED did not act directly in the mechanisms that modulate the smooth muscle, including the mediators released by muscle cells, epithelium, and resident cells.

Studies in animal models are important in order to contribute with new approaches, which may be used in humans in the future. In this context, based on our recent and earlier studies, we believe that photobiomodulation seems to be a promisor therapy to treat ALI. However, we still have much aspects to consider for its utilization in humans, including dosimetry, time of irradiation, barriers that the light need to penetrate, and skin color among others.

In mice, the visible red light in the range of 660 nm has a good penetration as we showed here and in other studies. However, in humans, this light could not penetrate easily, if we consider the area, and the thickness of tissues, including skin, thorax, and muscles. Perhaps in humans the most appropriate light is the infrared for penetrating more deeply. Despite of many differences between animals and humans, the importance of animal experimental models as a subsidy for the application in humans is indisputable.

Our results have shown that LED treatment was able to attenuate acute lung inflammation induced by sepsis, interfering systemically in the mobilization of cells from their reserve compartments as blood and mainly bone marrow. Importantly, even though two irradiations were performed after 2 and 6 h after LPS injection, the effects of the LED influence in changes up to 7 days after. Further, we note that the LED modulated IL-17A, IL-6, and lipoxin A4. Thus, this study may provide support for the understanding of the mechanisms involved in

the resolution of ALI, as well as propose the therapeutic adjuvant for this important condition.

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Compliance with ethical standards

Competing interests The authors declare that there are no conflicts of interest.

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