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IL-37 expression improves renal function after ischemia and reperfusion in mice model

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Abstract

Renal ischemia is a major problem in the world that lead to renal failure for which no effective treatment is available. Renal ischemia involves a robust inflammatory response, involving up-regulated chemokine expression and leukocyte accumulation, contributes to the mechanism of renal injury and renal failure. IL-37 is a new human cytokine and has an anti-inflammatory function. Currently, it is unknown whether IL-37 suppresses renal inflammatory response to ischemia. We tested the hypothesis that expression of human IL-37 in mouse protects the renal against ischemic injury through suppression of the renal inflammatory response.

IL-37 Tg and WT mice were subjected to right renal nephrectomy to induce unilateral model of ischemia the microvascular clamp was positioned around the left renal pedicles. Serum sampling for measurements of TNF-α, IL-1β, Caspase3, MDA, HMGB1, urea and creatinine. Hematoxylin-eosin staining for histological analysis. The resulted data showed that IL-37 has anti-inflammatory effects in renal IRI as evidenced by significant reduction of the inflammatory markers levels TNF-α, IL-1β and HMGB1. IL-37 has potent antioxidant and anti-apoptotic effects with significant reduction in MDA and caspace-3 respectively.

Keywords: Renal ischemia, IL-37, TNF-α, IL-1β, Caspase-3

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Introduction

The process of inflammation and pathophysiological changes associated with a series of many events known as ischemia-reperfusion injury that culminate into apoptotic in addition to necrotic cell death. It is a common type of injury for many organs including heart, kidney, brain, intestine, and liver [1]. Renal ischemia-reperfusion injury (RIRI) is one of the primary causes that can increase the rates of acute renal failure, delayed graft function, also, early mortality in patients

experiencing kidney transplantation [2]. It results from a generalized or localized reduction of oxygen and nutrient providing in addition to waste product removal from cells of the [3].

In spite of advances in therapeutic strategies, acute kidney injury (AKI) remains with high morbidity and mortality rates especially in those admitted to the intensive care unit (ICU) and increase the financial burden [4]. Generally, the death rates reported to be in the 30%-70% range there are chronic consequence regardless of the possibility that the patients survive their acute illness, with a high danger of developing chronic kidney disease (CKD) and end-stage renal disease (ESRD) [5], there is a critical need to therapeutic drug to fight this disease.

In patients with AKI show that the elevation in plasma proinflammatory cytokine concentrations the mortality was increased [6]. The pathogenesis of acute kidney injury as an inflammatory mechanism accompanied by releasing of tubular and vascular factors. In the mechanism of injury, the inflammation is thought to play a vital role in the AKI [7]. In the migration and recruitment of cells the vascular endothelium component involvement into sites of inflammation [8].

There are several processes in the immune system to distinguish the destructive pathogen, as an example is the pattern recognition receptors toll like receptors. (TLRs) and the particular receptors of the adaptive immune system can start reactions to quickly take out intrusive pathogens. These receptors have the ability to distinguish host cells that are injured or endogenous ligands. [9]. They can react with a protein after I/R which its structure is adjusted by ischemic injury or elements that are customarily sequestered nevertheless they are presented in response to ischemia. The immune cells have a different process for recognition such as stimulation by T cell receptors, might be critical in the pathogenesis of ischemic ARF [10]. Through the development of ischemia in the ARF the T cell association appears to happen [11], nonetheless, they show as early stimulators of the inflammatory reaction.

IL-37 formally called IL-1F7 [12] is the only member of IL-1 family which the mouse homolog is not detected yet [13], first identified in silico research in 2000 and has five different splice variants IL-1F7a–e [14] only IL-1F7b and -c containing exons 1 and 2 express an N-terminal prodomain that includes a potential caspase-1 cleavage site [15], IL-37 transcripts are detected in lymph nodes, thymus, bone marrow, placenta, lung, testis, and uterus [16], the protein is found in monocytes, tonsil plasma cells, and breast carcinoma cells also was detected in synovial cells of patients with rheumatoid arthritis, in alveolar monocytes from patients with Mycobacterium avium infections, in foam-like cells of atherosclerotic coronary and carotid artery plaques, in psoriatic plaques, and in the lamina propria monocytes of patients with Crohn's disease ,and in monocytes of lupus patients with severe disease [17].

Some studies suggest that IL-37 binds to α chain of the IL-18 receptor in a non-competitive fashion [18], and this may explain some of the disparate biological effects that have been

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reported for mice deficient in the IL-18R. The biological properties of IL-37 are mainly those of down-regulating inflammation, as assessed in models where human IL-37 is expressed in mice. TGF-b and several Toll-like receptor (TLR) ligands induce production of high levels of IL-37 by PBMCs; proinflammatory cytokines such as IL-18, IFN-g, IL-1b, and TNF moderately increase IL-37 levels IL-37b and the transgenic mice are protected from LPS-induced shock via reductions in proinflammatory cytokines and the inhibition of DC activation [19]. To understanding the mechanism and role of expression of IL-37 in protects the kidney against ischemic injury we used IL-37 transgenic mice.

Materials and Methods

Animal

Male Transgenic IL-37 mice and wild type mice C57, body weight 22-30 g, were obtained from Jackson Laboratory acclimatized in a quarantine room for 2 weeks, and their age range from 8 to 12 weeks. All animal experiments were approved by the Animal Care and Research Committee, Hospital Israelita Albert Einstein, São Paulo, SP, Brazil. Animals received humane care in compliance with the “Guide for the Care and Use of Laboratory Animals” [DHEW Publication No. (NIH) 85-23, revised 1985, Office of Science and Health Reports, DRR/NIH, Bethesda, MD 20205]. The animals are divided in three groups of mice; the first group represents sham for control second group transgenic IL-37 and third group C57 wild type mice, ten animals in each group.

Experimental model of renal Ischemia /Reperfusion Injury

Mice were anesthetized by using intraperitonial injection of ketamine in a dose of 100 mg/kg and xylazine in a dose of 10 mg/kg. Under sedation (5-10min), rats were placed on its back, fixed their limbs and tail with stickers to ensure their stability during surgery. Hair in chest area was shaved and the skin disinfected. The reflexes were checked via pinching the tail and the hind feet to be sure that the rats are sufficiently anesthetized. Midline laparotomy incision was made to expose the abdomen, and in order to expose renal pedicles the intestines were retracted.
Right renal nephrectomy was done and to induce unilateral model of ischemia the microvascular clamp was positioned around the left renal pedicles. The total time of clamping was 30 min and through this procedure the abdomen was covered with warm and moist gauze. The blood flow to the kidney was returned after the clamp was removed and this could be confirmed visually. Then the abdominal cavity incision will be closed in two layers. The animals were returned to their cages and allowed to get better with food and water. In post-surgery after three hours, the

animals were euthanized and both blood as well as tissue samples were collected for analysis [20].

Animal scarification

Immediately after finishing the pressure volume loop measurement, the mouse was sacrificed, starting by injection of equal volume of thiopental and heparin intraperitoneal in doses ranging from 100µl to 200 µl for each one, after giving good time for the animal to go into deep anesthesia, the mouse is positioned and taped and the chest is opened in flap like manner revealing the heart then a needle of the syringe is introduced into right ventricle to aspirate around 0.5 ml of blood for plasma analysis. After that the kidney is cut from the great vessels.

Blood Sampling

At the end of the experiment, blood was gathered from the heart. The sample of blood was placed in a plane tube at 37 C without anticoagulant and left for 30 minutes then it was centrifuged at 3000 rpm for 10 minutes, then serum obtained to be used for the determination of serum TNF-α, IL-1β, MDA, Caspase-3, HMGB1, urea and creatinine levels by enzyme-linked immunosorbent assay (ELISA). The kit of Elisa commercially available was used according to the manufacturer's instructions.

Tissue Sampling for Histopathology:

The kidney was washed with normal saline to remove any blood, the part of tissue was taken from the left kidney sample and fixed in 10% formalin and processed by routine histological methods and embedded in paraffin block [21]. The tissue slide sections were cut about 5 µm-thick horizontal and stained with hematoxylin- eosin (H&E) then sent to histopathologic for subsequent histological examination. After fixation, an investigator who was blinded to the experimental treatment groups performed evaluation of scores. Tissue sections were examined by light microscope and graded for degeneration/necrosis. By using quantitative measurements for the assessing scoring system of tissue damage [21]. The tubular damage was identified as swelling of tubular epithelial, brush border losing, vacuolar degeneration and formation of cast. The degree of the renal damage was described via the subsequent criteria 0, represents normal; 1, represents <25% of the damage of the tubules; 2, represents 25%_50% of damage of the tubules; 3, represents 51%-75% of damage of the tubules; 4, represents 75%-100% of damage of the tubules.

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Measurement of IL-1β, Caspase-3, Malondialdehyde (MDA) and high mobility group box protein 1(HMGB1)

The microtiter plate has been supplied as pre-coated with antibody specific for IL_1β. Then samples are added to the suitable microtiter plate wells with a biotin-conjugated antibody specific to IL-1β, Caspase-3, Malondialdehyde (MDA), high mobility group box protein 1(HMGB1). Next, Avidin conjugated to Horseradish Peroxidase (HRP) is added to each microplate well and incubated. After TMB substrate arrangement is included, just those wells that contain IL1β, Caspase-3, Malondialdehyde (MDA), high mobility group box protein 1(HMGB1), biotin-conjugated counter acting agent and protein conjugated Avidin will display an adjustment in color. The catalyst substrate response is ended by the expansion of sulphuric acid arrangement and the color change is measured spectrophotometrically at a wavelength of 450nm ± 10nm. The grouping of IL-1β, Caspase-3, Malondialdehyde (MDA) and high mobility group box protein 1(HMGB1) in the specimens are then dictated by looking at the O.D. of then examples to the standard curve.

Measurement of Urea

Enzymatic and colorimetric method based on the specific action of urease which hydrolysis urea in ammonium ions and carbon dioxide. Ammonium ions then form with chloride and salicylate blue-green complex. This coloration, proportional to urea concentration in the specimen, is measure at 600 nm.

Measurement of creatinine

Colorimetric reaction (Jaffe reaction) of creatinine with alkaline picrate measured kinetically at 490nm without any pretreatment step. This reaction has been improved (specificity, speed and adaptability) by the development of an initial rate method.

Histopathological Evaluation

Kidney section was examined by light microscopy at corticomedullary junction and scored according to quantitative scale measurements of tissue damage designed by [21] to assess the severity of renal damage. Tubular damage was recognized as tubular epithelial swelling, loss of brush border, vascular degeneration, necrotic tubules, cast formation and desquamation. The slide section divided into 10 intersections. This done by a pathologist who was unaware of the treatment conditions. a score from 0-4 was given for each tubular profile involving the following criteria:

0 = normal histology

1 = area of damage < 25% of tubules (mild)

2 = damage involving 25% -50% of tubules (moderate)

3 = damage involving 51%- 75% of tubules (severe)

4= damage involving 76%-100% of tubules (highly severe)

The total score for kidney section was calculated by the summation of all 10 intersections with a maximum score of 40 and according to the total severity score.

Statistical Analysis

Data were summarized, analyzed and presented using two software programs, the Statistical Package for Social Sciences (SPSS version 20) and Microsoft Office Excel 2010. Variables included in the present study were initially described in terms of number of cases, median, mean, standard deviation (SD) and range; then they were subjected to two tests of normality distribution Kolmogorov-Smirnova and Shapiro-Wilk tests. Mann Whitney U test was used to study difference in median rank values between any two groups. Result were regarded as (significant, highly significant and extremely significant level) at (P≤0.05, P≤0.01, P≤ 0.001) respectively.

Results

Mean serum level of TNF- α in wild mice C57 group was significantly higher than that of sham group, (81.11 ±10.00 pg/ml versus 20.21 ±2.55 pg/ml p≤0.05; the mean was significantly lower in IL-37 mice group in comparison to that of the C57 group. Figure 1.

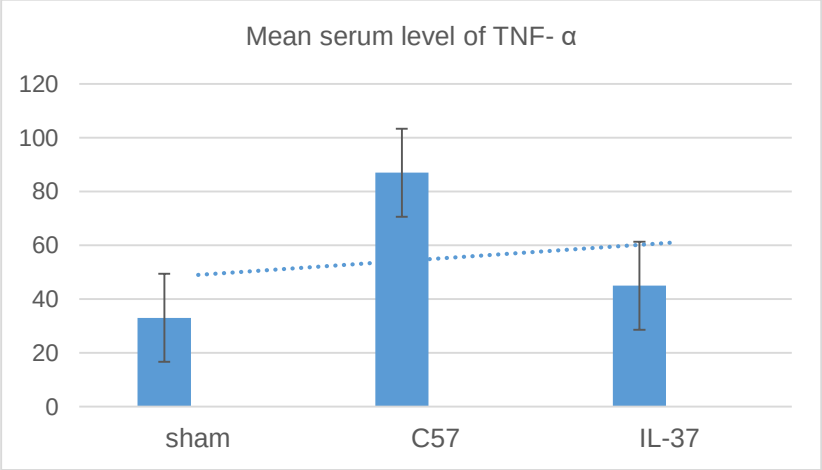

Figure 1.

Mean serum level of TNF-α in the experimental groups p≤ 0.05

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Mean serum level of IL-1β in C57 mice group was significantly higher than that of sham group, (117.81 ±151.06 pg/ml versus 32.76 ±30.36 pg/ml p≤0.05, the mean was significantly lower in IL-37 tg mice group, 47.15 ±36.08 pg/ml. Figure 2.

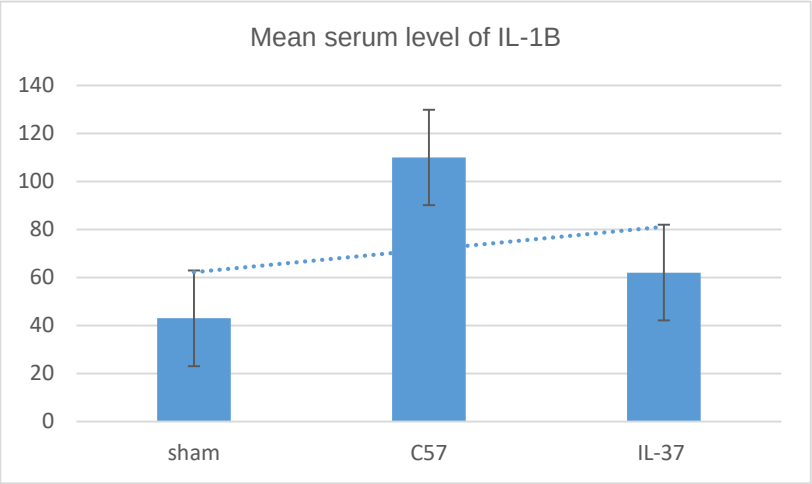

Figure 2.

Mean serum level of IL-1β in experimental groups, p≤0.05

Mean serum level of caspase-3 in C57 mice group was significantly higher than that of sham group, 4.48 ±1.03 pg/ml, p≤ 0.01; the mean was significantly lower in IL-37 tg mice group, 9.85 ±0.56 pg/ml. Figure 3.

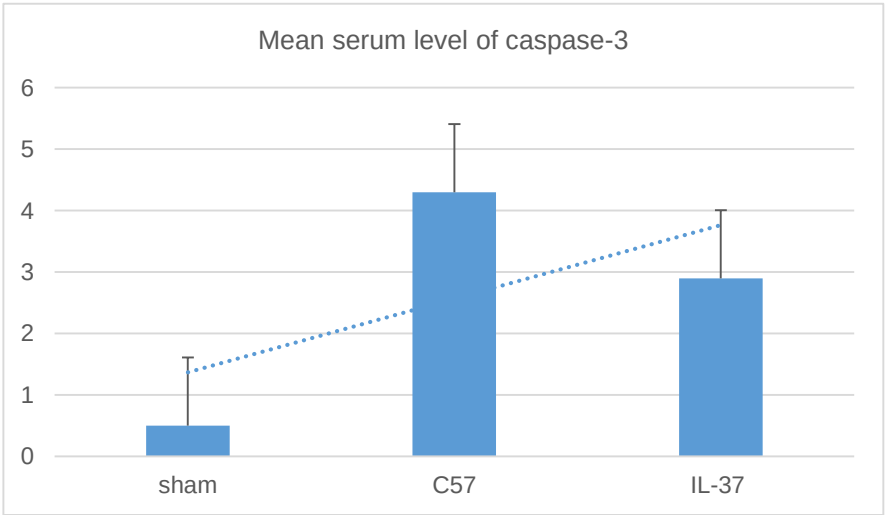

Figure 3.

Mean serum level of caspase-3 in experimental, p≤ 0.05

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Mean serum level of MDA in C57 mice group was significantly higher than that of sham group, 68.31 ±1.35 pg/ml p≤ 0.01; the mean was significantly lower in IL-37 tg mice group, 36.81 ±0.26 pg/ml. Figure 4.

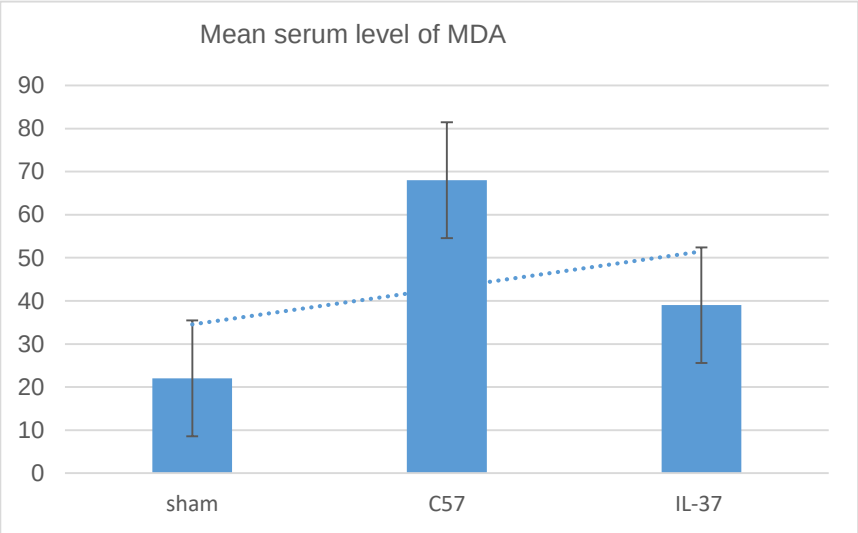

Figure 4.

Mean tissue level of MDA in experimental groups, p≤ 0.01

Mean serum level of HMGB1 in C57 mice group was significantly higher than that of sham group, 2890.31 ±1.35 pg/ml p≤ 0.01; the mean was significantly lower in IL-37 tg mice group, 2000.81 ±0.16 pg/ml. Figure 5.

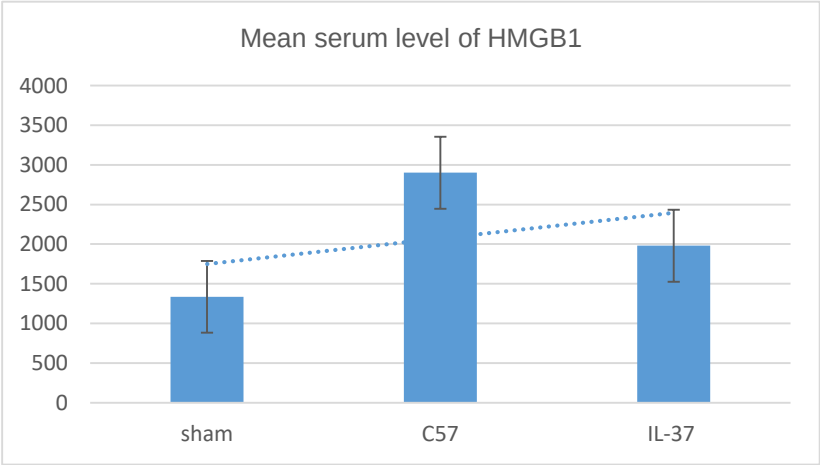

Figure 5.

Mean serum level of HMGB1 experimental groups, p≤ 0.01

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Mean serum level of urea in C57 mice group was significantly higher than that of sham group, 98.61 ±1.15 pg/ml p≤ 0.01; the mean was significantly lower in IL-37 tg mice group, 50.81 ±0.26 pg/ml. Figure 6.

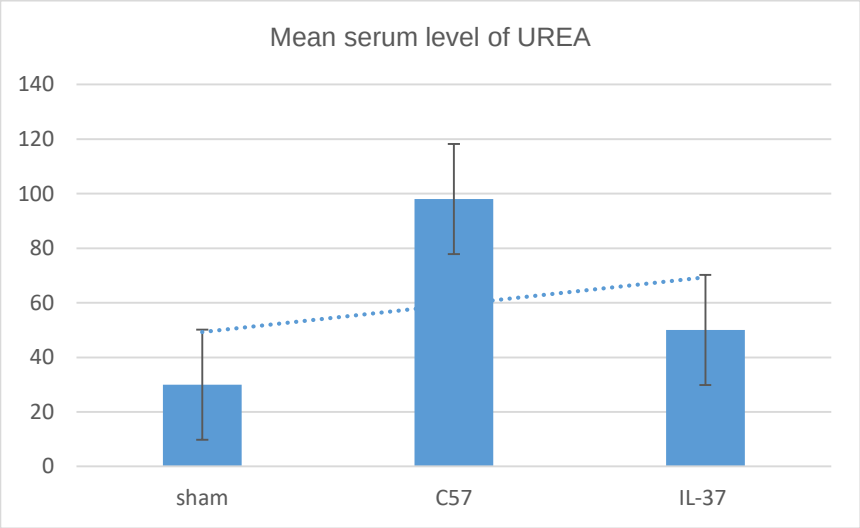


Figure 6.

Mean serum level of urea in experimental groups, p≤ 0.01

Mean serum level of creatinine in C57 mice group was significantly higher than that of sham group, 168.31 ±1.12 pg/ml P=0.004; the mean was significantly lower in IL-37 tg mice group, 98.81 ±0.16 pg/ml. Figure 7.

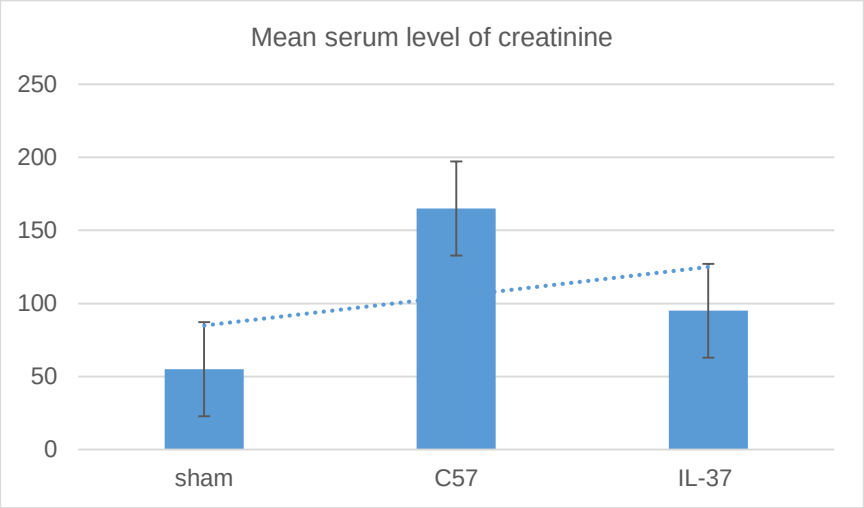
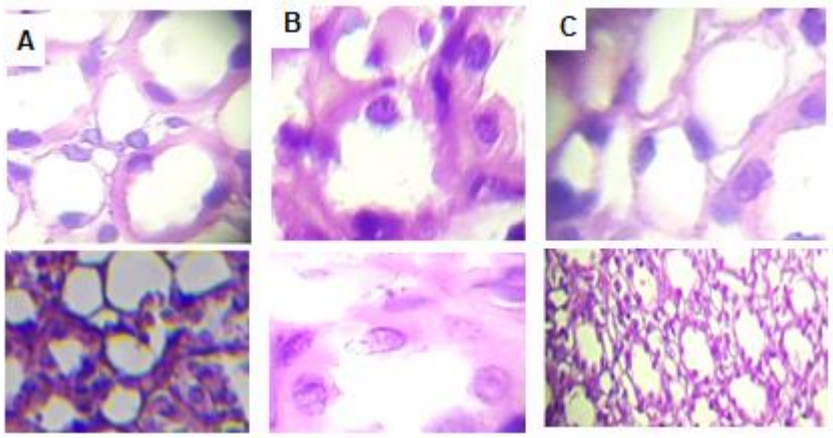


Figure 7.

Mean serum level of creatinine in experimental groups, P=0.004

Comparison of histological scores among experimental groups

Mean histological score was significantly higher in in C57 mice group was significantly higher than that of sham group, 168.31 ±1.12 pg/ml P=0.004; the mean was significantly lower in IL-37 tg mice group, 98.81 ±0.16 pg/ml. Figure 8. Mean histological score of vehicle group was 1.75 ±0.43, with no significance difference from control group (P=1.000) however it was significantly higher than that of ghrelin group (P=0.006), as shown in table 3-9 and figure 3-13.



Photomicrograph of kidney section of rats shows: A/Sham, B/C57 and C/ IL-37 after Renal injury showing increased eosinophilia, cytoplasmic and nuclear degeneration and cast formation in C57 mice after Renal injury. H and E stain (40 X).

Discussion

Renal I/R injury is a life threatening condition and its manifestations, range from increase in serum level of urea and creatinine to anuric kidney failure. Clinically renal I/R is the leading cause of acute kidney injury associated with different cases involving decrease of cardiac output, renal vascular obstruction, and renal transplantation [22]. So, there is an urgent medical need for a specific therapeutic agent.

The effects of the IL-37 used in present study on I/R was compared with that found by other studies in order to illustrate its effectiveness and to explain how it can have exerted its effect on IRI and improve kidney functions or protective role to decrease renal injury in rat model.

In this study we found that TNF-α and IL-1β serum and tissue levels were significantly increased ($p<0.05$) in ischemia I/R group more than that in sham group and this is consistent with study [23]. And the explanation of this elevated level of cytokine through I/R is that these indicators are

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produced from macrophages and monocytes [24] and ischemia reperfusion lead to infiltration of macrophage to the renal parenchyma [25]. Local production of TNF-α has been implicated in the pathogenesis of renal IRI by Its released from the kidney in response to injury and thereby oxidants will be released following reperfusion activate P38 mitogen activating protein kinase (P38 MAPK), NF Kappa B and TNF-α transcription factor and these cause an increase in TNF-α synthesis which induces glomerular fibrin deposition in addition to cellular infiltration and vasoconstriction resulting in a decrease of the GFR [26].

Nevertheless, an evidence shows that glomerular mesangial cells are an essential further source for production of TNF-α [27]. Lipopolysaccharide (LPS; endotoxin) which has been found to induce isolated mesangial cells or glomeruli to produce TNF, even after rats were deprived of bone marrow-derived cells by whole body irradiation LPS-stimulated TNF production has been localized to glomerular mesangial cells. So the kidney itself is capable of producing TNF in response to LPS, TNF, or interleukin one (IL-1).

The early changes occurring after IRI which are rapidly causing elevation of P-selectin that is translocated to endothelial cell surfaces within 5 min of revascularization of the organ, initiating steps leading to tethering of PMNs to the vascular intima [2]. There was a significant ($p<0.05$) increase in serum and tissue levels of IL-1β, in local production of IL-1β and/or TNF by these leukocytes induces P- and E-selectin expression on endothelium which continues the cascade of events which increase cell adherence and infiltration of the injured tissues. The improvement in renal function was followed by a lower expression of IL-1b, IL-6 and TNF-α [5].

In present study the results revealed that HMGB1which is a potent proinflammatory cytokine that contributes to the pathogenesis of diverse inflammatory and infectious disorders was significantly higher in I/R group ($p<0.01$) than in that of sham group and this consistent by [28]. The HMGB1 stimulate proinflammatory responses through TLR4.

Our result agrees with other study which confirmed upregulation of HMGB1 and HMGB1-triggered downstream cytokines and chemokines in IRI in kidney, reliable with a proposed role for HMGB1in elevating kidney injury [6].

Ischemia is an inflammatory process associated which after reperfusion emerged release of HMGB1 and localize in renal tubules, peritubular capillaries and glomeruli where the renal cells might be more predisposed to ischemic injury as proved by the previous study [30].

Apoptosis is one of a series events that occur during renal IRI as a result of hypoxia which is well-known stressors, triggering apoptosis in various cell type.

Our study showed that the mean of I/R group for serum and tissue caspase-3 was significantly ($P<0.05$) higher than that in sham group. In the kidney, in human and animal models focused on the ischemia to detect the hypoxia that induced the renal cellular and tissue damage in chronic renal diseases beside apoptosis [3].

The data of present study are consistent with that of other studies which revealed that caspase-3 activated through renal I/R injury.

There is another study show that renal I/R injury cause an elevation of caspase-3 due to chronic hypoxia in tissue damage. Apoptosis and caspaces-3 are not only involved in the long term renal ischemia reperfusion injury, but they also mediate the different effects of immunosuppression in this model [31].

In this study, I/R showed significant change ($P<0.05$) in serum and tissue MDA level when we compared with sham group, this reflect that there is an elevation in production of ROS that released as a result of increase renal content of lipid peroxidation malondialdehyde in cortical mitochondria after renal ischemia and reflow and this study is similar to other studies.

The normal cellular defense mechanism against free radical injury is supplied by enzymatic (catalase, superoxide dismutases, and glutathione peroxidase) and non-enzymatic (GSH, α-tocopherol, vitamin C, and urate) free radical scavenging systems, exisiting in the cell [32].

Thus, the use of antioxidants therapy provide improvement against kidney diseases. Oxygen free radical that induced damage after ischemia has been studied in myocardium, brain, and small intestine and liver [5].

In this study there was a significant increase in serum urea and creatinine levels ($p<0.05$) in control group as compared to that of sham group as a result to the decrease glomerular filtration rate, these results are in agreement with [6].

In I/R group, most intersections of renal tissue of rats showed tubular epithelial swelling, loss of brush border, vascular degeneration, necrotic tubules, cast formation and desquamation. these changes were in agreement with other study [4, 7, 22, 30] reported that unilateral renal pedicle clamping for 30 minutes followed by 24 hours of reperfusion in mice would cause renal tissue dysfunction and worse histology after bilateral pedicle clamping with proximal tubular injury, loss of brush-border, proteinaceous casts, interstitial widening, and necrosis and these findings agree with the present study.

The severity of histological renal damage is dependent on ischemia time (30 minutes of unilateral IRI). Caused prominent renal damage and sever loss of structure [8, 11].

In this study, I/R causes significant increase ($P<0.05\%$) in serum and tissue level of TNF-α, IL-1β, HMGB1 which are proinflammatory cytokines That cause adhesion, transmigration of polymorphonuclear into kidney tissue and production of ROS that was involvement in the pathogenesis of acute tubular necrosis (ATN) as proved in the study [33].

In addition to another mechanism that accomplished in the present study by the release of proinflammatory cytokine which preserve to increase the level of tissue damage and induction tissue dysfunction and or apoptosis which agree with [4].

This study shows that the use of IL-37 mice. before induction of ischemia and immediately at the reperfusion time caused significant lowering ($p<0.05$) in serum levels of TNF-α, IL-1β and HMGB1 as compared with that in I/R group. These findings are consistent with other study [22], which showed that IL-37 inhibit expression of proinflammatory mediators TNF-α, IL-1β and IL-6 also has a role in the regulation of the immune response through its expression in T-lymphocytes and monocytes. Release of inflammatory cytokines by immune cells have be shown in most common diseases and tissue injury.

The HMGB1 rapidly translocate from its normal site of residence in the nucleus to the cytoplasm and out of cells when stimulation occur by injury or by damage signaling molecules. The present study showed that the mean of serum and tissue levels of HMGB1 significantly were decreased ($P<0.01$) in IL-37 group. The significant characteristic of HMGB1 is its fast release after cellular injury suggesting that HMGB1 may play a major role in the early stages of damage to the renal tissue following injury.

Other study agreement with the results in that the proinflammatory effect of HMGB1 releasing from macrophages and monocytes and more other cell type involving endothelial cells that upon stimulation initiates the exacerbation of signal cascade so induction further tissue damage following ischemic insult [5, 9, 11].

The present study showed that IL-37 caused significantly ($p\leq0.01$) decrease in the mean of serum and tissue levels of MDA and this confirmed that IL-37 has antioxidant effect which provide its protective effect against kidney damage these results findings agree with many evidence that shown antioxidant effect of IL-37 in mice.

IL-37 prevents lipid peroxidation and raises antioxidant enzyme activities (glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase (CAT)) and glutathione (GSH) content in the rat testes [33] and ovaries. In other hand other resulted data showed that IL-37 has antioxidant effect on tissue injury, and significantly decrease MDA level as shown by other. reduced MDA levels in the alendronate-induced gastric tissue injury in rats.

The explanation of these findings are that IL-37 decreased formation of reactive oxygen species (ROS) as revealed in. It inhibits vascular superoxide production and oxidative stress in hypertensive rats by inhibition of vascular NADPH oxidase [32]. Therefore, it can be concluded that IL-37 preserves the membrane of renal tissue against oxidative stress and lipid peroxidation.

The serum level of urea and creatinine are significantly decrease ($p\leq0.01$) in IL-37 group as compared with that of I/R group.

These findings agree with most of evidence that proved the ability of IL-37 to cause direct effect in reduction of serum levels of urea and creatinine [33].

These findings established the protective role of IL-37 to improve renal function and decrease tissue injury by decrease the level of proinflammatory cytokines mediators such as TNF-α and

IL-1β [34] and decreased the production of free radicals in addition to ROS and NO by inhibition of NOS and lipid peroxidation [34], thus decrease the cellular injury.

The mean of total severity scores of the sections of kidney in IL-37 was significantly decrease as compared to I/R group (P≤0.01) and that suggest significant degree of kidney protection from I/R injury.

IL-37 seems to serve as an attractive agent with therapeutic characteristics that improve the function of kidney against tissue damage and provide strong data for potential therapeutic effects applies in the many field of medical research.

Conclusions

According to the findings of the present study the following can be concluded; IL-37 has protective effect on the kidney with significant amelioration of renal IRI as evidenced by preservation of renal histology with normal renal function parameters and significant reduction of markers levels of renal injury. IL-37 has anti-inflammatory effects in renal IRI as evidenced by significant reduction of the inflammatory markers levels namely (TNF-α, IL-1β and HMGB1).

IL-37 has potent antioxidant and anti-apoptotic effects with significant reduction in MDA and caspase-3 respectively.

Competing interests

The authors declare that they have no competing interests.

Ethical Committee

This work was approved by Middle Euphrates Neuroscience Center, and Faculty of Medicine/ University of Kufa.

Authors' contributions

All authors participated in the conception and design of the study, collected and analyzed the data, read and reviewed the final manuscript.

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