

Cytokine disbalance in the rats' kidneys following *Leiurus macroctenus* envenomation

Ruzhena Matkivska¹, Serhii Shchypanskyi^{2*}, Nataliia Raksha², Tetiana Vovk², Tetiana Halenova², Oleksandr Maievskyi³, Olexiy Savchuk², Liudmyla Ostapchenko²

¹Department of Descriptive and Clinical Anatomy, Bogomolets National Medical University, Kyiv, Ukraine.

²Department of Biochemistry, Educational and Scientific Center, Institute of Biology and Medicine, Taras Shevchenko National University of Kyiv, Kyiv, Ukraine.

³Department of Clinical Medicine, Educational and Scientific Center, "Institute of Biology and Medicine" of Taras Shevchenko National University of Kyiv, Kyiv, Ukraine.

ARTICLE INFO

Article history:

Received on: December 04, 2023

Accepted on: February 18, 2024

Available online: April 20, 2024

Key words:

Envenomation,
Inflammation,
Cytokine profile,
Scorpion venom,
Growth factors.

ABSTRACT

Scorpion envenomation is a challenge for the health-care system. The development of inflammation is very interesting yet at the same time, important effect of the scorpion venom, being indicative for the severity and progression of envenomation. Excretion of venom toxins and endotoxins by kidneys expectedly makes this organ a perfect target for the inflammation development. Therefore, this work was focused on the assessment of cytokine, growth factor (GF), and transcription factor profiles in the kidneys of rats, envenomated by scorpion *Leiurus macroctenus*. Using the ELISA method, we have shown that starting from the 3rd h of envenomation, the levels of most of assessed parameters were constantly rising, reaching the peak levels at 24 h; therefore, this period is likely the most stressful for the renal system in the aspect of envenomation. Furthermore, we have demonstrated that the relative concentrations of anti-inflammatory interleukin (IL)-4 and IL-8 were rising, while most of the pro-inflammatory cytokine levels were not, suggesting about the cytokine imbalance, which theoretically may lead to the insufficient immune response and potential tissue damage by the venom toxins. The elevated levels of GFs fibroblast GF-2, vascular endothelial GF, and epidermal GF can also be related to the tissue-destructive action of *L. macroctenus* venom.

1. INTRODUCTION

The problem of envenoming by scorpions becomes more aggravated year by a year. Climate changes, leading to scorpion populations spreading, as well as the rapid development of previously uninhabited lands by humanity cause more often tragical interactions with scorpions [1].

Even though many scorpions' venoms are comprised of dangerous toxins, in most cases, scorpion sting provides only local manifestations such as itching, hyperemia, local pain, edema, etc. [2]. Systemic effects of scorpion venoms, such as arrhythmia, hypertension, hyperglycemia, and cardiac failure, are considered to be related to the autonomic nervous system hyperactivation, yet systemic inflammation development (as a result of immune cells activation) can also be a reason of many typical clinical symptoms of scorpion sting [3].

The production of pro-inflammatory, anti-inflammatory cytokines, and various growth factors (GFs) is a typical immune response of organism to the scorpion venom components and consequences of their activity [4]. While the function of cytokines and chemokines lies mostly in "communicating" between immune cells, which leads to the efficient annihilation of the antigen, GFs facilitate "repairing" of the damaged tissues after the inflammation is resolved [5].

Among all organs that suffer during systemic scorpion envenomation, high concentrations of venom toxins and products of tissue protein degradation expectedly accumulate in the kidneys, making this organ a site for the inflammation development, which in turn may lead to the renal dysfunction [6]. We have previously shown the negative effects of the *Leiurus macroctenus* venom (LmV) on rats' kidneys including protein homeostasis disruption, elevated levels of proteolytic activity, and matrix metalloproteinases' contents [7,8]. To expand the knowledge of the LmV effects on kidneys, we have examined relative levels of cytokines, namely tumor necrosis factor- α (TNF- α), interleukin (IL)-1 β , IL-4, IL-6, IL-8, IL-10, interferon- γ (IFN- γ), transcription factors (TFs) nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), hypoxia-inducible factor-1 α (HIF-1 α) and GFs vascular endothelial GF (VEGF), fibroblast GF-2 (FGF-2), and epidermal GF (EGF) in the kidneys of envenomated rats.

*Corresponding Author:

Serhii Shchypanskyi,

Department of Biochemistry, Educational and Scientific Center, Institute of Biology and Medicine, Taras Shevchenko National University of Kyiv, Kyiv, Ukraine.

E-mail: shchypanskyi.s@ukr.net

2. MATERIALS AND METHODS

2.1. Maintenance of the Scorpion Specimens

In the experiments, we have been using 10 mature *L. macroctenus* scorpions that had been previously kept in Mark Stockmann's private collection in Ibbenbüren (Germany). The animals were housed in the individual translucent plastic boxes, layered by 1 cm of sand (Exo Terra «Desert Sand»), aeration of boxes was achieved by holes in them. Once a week, a water bowl in each box was refilled with distilled water, and one cockroach (*Shelfordella lateralis*) was given to each scorpion. Boxes with animals were placed in constant conditions: Temperature: 25°C–35°C; humidity: 50–60%; lighting conditions: Natural.

2.2. Venom Collection

The manipulations of venom obtaining we have described previously [7], and venom's lethal dose-50 (LD₅₀) determination was achieved using Ozkan and Filazi's method [9]. The obtained samples of venom were aliquoted and stored frozen at temperature of –20°C.

2.3. Murine Envenomation Modeling and Obtaining of Kidney Homogenates

All experiments on animals were conducted according to the Guide for the Care and Use of Laboratory Animals, and the experiments were approved by the Ethical Committee of Taras Shevchenko National University of Kyiv (protocol №2 approved August 19, 2021). In the experiments, we have used 60 male rats (180 g ± 3 g) that were intramuscularly injected with venom solution (0.5 mL, LD₅₀), and the control group, 13 rats, was in the same way injected with saline solution (0.5 mL, 0.9%).

To evaluate the dynamic changes of assessed parameters, the euthanasia of rats was performed in the periods of 1 h, 3 h, 24 h, and 72 h following the venom injection, after which, the rats' kidneys were isolated and homogenized at +1–4°C. For the homogenates' preparation, we have used 0.05 M Tris-HCl (pH 7.4) buffer with 0.14 M NaCl and 0.001 M EDTA in the mass proportion tissue: buffer as 1:9. Obtained homogenate was centrifuged at 600 g for 15 min and collected supernatant was centrifuged again at 15,000 g for 15 min. Obtained homogenate was aliquoted and stored frozen in the liquid nitrogen.

2.4. Immunoenzyme Analysis (ELISA)

The determination of the IL-4, IL-1β, TNF-α, IL-6, IL-10, IL-8, IFN-γ, HIF-1α, NF-κB, FGF-2, VEGF, and EGF contents in rats'

kidneys homogenates was performed through immunoenzyme assay (ELISA). Homogenate samples were incubated at +4°C overnight in sterile ELISA plate wells. Next, they were washed 3 times with washing buffer (0.05 M Tris-HCl (pH 7.4) with 0.14 M NaCl and 0.05 % v/v Tween-20) and were blocked by 5% non-fat dry milk solution, being incubated at +37°C for 1 h. After that, we washed the wells 3 times with washing buffer, after that, they incubated at +37°C for 1 h with appropriate primary antibodies (Sigma-Aldrich, Germany) solutions (dilution 1:3000). After washing the wells from unbound antibodies, the HRP-conjugated secondary antibodies (Sigma-Aldrich, Germany) with 1:7000 dilution were added and incubated at +37°C for 1 h. Next, the mixture of o-phenylenediamine (0.4 mg/mL) in 0.05 M citrate-phosphate buffer and 30% H₂O₂ was added to the wells as a substrate. We terminated the reaction in 10 min by adding 3 M H₂SO₄ in the wells. Optical density was measured at 492 nm using a microplate reader.

2.5. Statistical Analysis

The obtained results were analyzed and visualized using OriginPro v9.5 software and expressed as mean ± standard error of mean. Graphical materials were prepared using Krita software. The significance of differences between the control and experimental groups was calculated by unpaired *t*-test through OpenEpi software. The results were believed as statistically significant when *P* < 0.05.

3. RESULTS

From the immunological point of view, the components of scorpion venoms are very powerful antigens and immunogens that can trigger adaptive and innate immune responses. The development of systemic or, at least, local inflammation is inherent to many studied scorpion venoms, yet the cytokine profile and the severity of the inflammation processes in the victims' organisms depend on the venom composition, which in turn varies among scorpion species [10].

This study was dedicated to investigate the levels of pro-inflammatory as well as anti-inflammatory cytokines in the kidneys of rat envenomated by *L. macroctenus*. As it can be seen in the Figure 1a, envenomation leads to the visible decrease in the levels of IL-6 and TNF-α (which are pro-inflammatory) starting from the 3rd h after venom injection. At 24 h, the relative levels of TNF-α and IL-6 were 78% and 67% of the control values respectively, however, in the next 48 h, their contents tend to stabilize, reaching nearly control values. In contrast, we have observed statistically significant elevation of IFN-γ levels starting from the 3rd h and

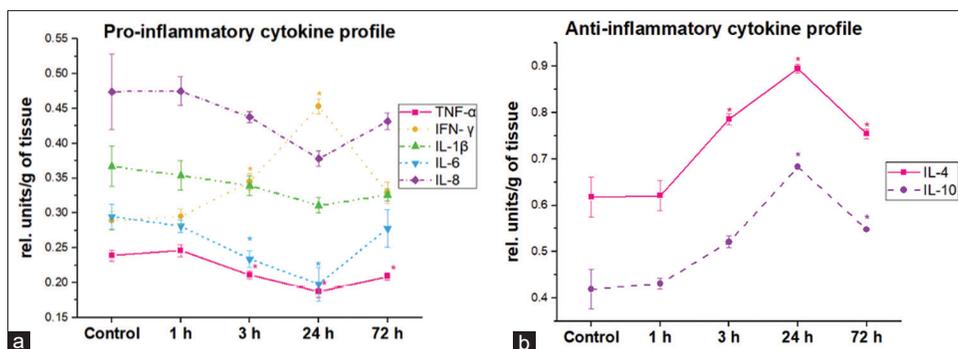


Figure 1: Cytokine profile of rat's kidneys following *Leirus macroctenus* envenomation: (a) pro-inflammatory cytokines, (b) anti-inflammatory cytokines (mean ± standard error of mean; *n* = 5). **P* < 0.05, comparing to the control animals.

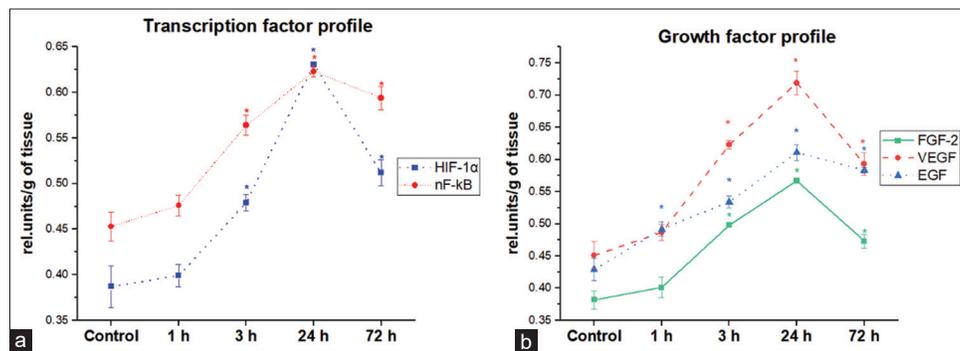


Figure 2: Transcription factor (TF) and growth factor (GF) profile of rat's kidneys following *Leirus macroctenus* envenomation: (a) TFs, (b) GFs (mean \pm standard error of mean; $n = 5$). * $P < 0.05$, comparing to the control animals.

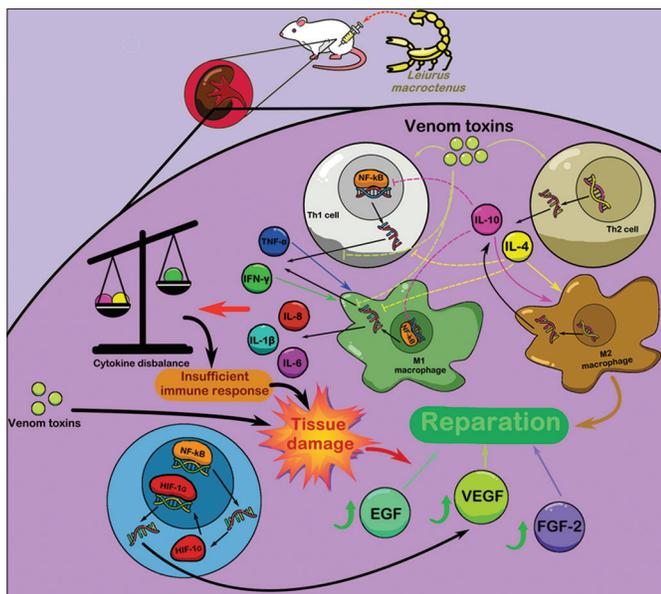


Figure 3: The illustrative summary of *Leirus macroctenus* venom effects in the context of inflammation in kidneys of envenomated rats. Venom toxins trigger the activation of Th2 and Th1 cells, which synthesize anti- and pro-inflammatory cytokines, respectively. These molecules may activate macrophages that also produce certain types of cytokines. Hypothetically, venom toxins themselves or/and anti-inflammatory interleukin (IL)-10 and IL-4 can downregulate the pro-inflammatory cytokine synthesis, leading to cytokine disbalance and, therefore, weak immune response, contributing to the potential kidney damage. At the same time, development of tissue hypoxia, which is closely related to the inflammation, triggers the hypoxia-inducible factor-1 α -dependent synthesis of vascular endothelial growth factor (GF), which in turn, with epidermal GF and fibroblast GF-2 can be involved in the preparation of damaged tissue.

reaching the maximum value at 24 h of envenomation – about 157%, comparing to the control group. Nevertheless, we have not observed any statistically significant changes in the levels of the IL-1 β and IL-8.

According to the [Figure 1b](#), relative levels of the anti-inflammatory IL-10 and IL-4 in the kidneys of envenomated rats have been

constantly rising for the first 24 h of envenomation and the peak values of these parameters were nearly 163% and 145% of the control values, respectively. As in the case of pro-inflammatory cytokines, in 72 h after venom injection, concentrations of the anti-inflammatory cytokines were rapidly approaching the control values.

We also have measured the changes in the relative concentrations of pro-inflammatory TFs, namely HIF-1 α and NF- κ B, during envenomation. According to the results, presented in the [Figure 2a](#), LmV triggers the higher, comparing to the control group, expression of HIF-1 α and NF- κ B in the kidneys of envenomated rats. As it was mentioned above for the other parameters, the most significant effects can be observed in the period of 3–24 h of envenomation. The peak concentrations of HIF-1 α and NF- κ B (163% and 138% of the control values, respectively) were expectedly measured in 24 h following envenomation. For the next 48 h, concentrations of these proteins had been decreasing, yet as it can be seen in the [Figure 2a](#) that the rate of HIF-1 α level decrease is much more rapid than that observed for NF- κ B.

The situation is rather similar for the levels of GFs FGF-2, VEGF, and EGF. Starting from the 3rd h of envenomation, concentrations of FGF-2 and VEGF were increasing and in 24 h reached 148% and 159% of the control values, respectively [[Figure 2b](#)]. In the case of EGF, we have noticed the statistically significant changes starting from 1 h after venom injection, with rapid increment for the next 23 h and maximal value of 142% of control concentration at 24 h. As for the other parameters, from 24th to 72nd h of envenomation, concentrations of these GFs were constantly declining.

4. DISCUSSION

Inflammation on the local or systemic levels is a typical response of organism to the presence of foreign structures or molecules, such as components of scorpion venoms. The release of pro-inflammatory cytokines usually facilitates enhanced utilization of pathogens through different mechanisms, while anti-inflammatory cytokines control the activity of the former, compensating their levels. The correlation between levels of anti- and pro-inflammatory cytokines defines the progression or resolution of inflammation and could even be an indicator of severity of the scorpion envenomation [[11](#)].

In this study, the significant changes in the levels of anti-inflammatory IL-10 and IL-4 in the kidneys of rats envenomated by *L. macroctenus* were revealed. IL-4 is known as a multifunctional anti-inflammatory cytokine, which participate in differentiation of many immune cells [12]. The importance of IL-4 also lies in the polarizing effect on macrophages, switching them to M2a phenotype, which is so-called "tissue-reparative phenotype." These polarized macrophages can usually be found in the tissues during different pathological states, including acute kidney injury (AKI) [13]. In our study, renal levels of IL-4 were elevated, which can be associated with rising amounts of pro-inflammatory cytokines, like IFN- γ , but it also could be a response on a kidney injury through M2a macrophage differentiation. IL-10 is also a multipotent anti-inflammatory cytokine; moreover, it is the key cytokine in an anti-inflammatory response. This molecule is responsible for controlling the essential metabolic pathways [14], and, as it turns out, it can stimulate M2a macrophage differentiation, like the IL-4 does [15]. We have shown that envenomation by *L. macroctenus* can elevate IL-10 levels in rats' kidneys; moreover, as in the case of IL-4, the significant changes can be observed from 3rd h of envenomation with peak levels at 24 h. These results are consistent with the opinion that excretion of scorpion toxins by kidneys accounts for 1 day after the scorpion sting [3]; thus, the local inflammation development in this period results in high concentrations of IL-4 and IL-10. There are also reports about rising concentrations of IL-10/IL-4 in murine models as a response to scorpions' *Crotalus durissus cascavella* [16] and *Hadruidoies lunatus* [17] venoms.

Even though risen levels of pro-inflammatory cytokines are quite common immune response to scorpion venoms [18], in our study, only IFN- γ levels were increased (mostly at 24 h of envenomation), while we did not observe any significant changes in the levels of IL-1 β and IL-8. Moreover, we have found that the concentrations of IL-6 and TNF- α were decreasing from 3rd to 24th h of envenomation, and this phenomenon can be explained at least by 2 mechanisms. First, IL-4 and IL-10 in high concentrations can synergistically inhibit the synthesis of pro-inflammatory cytokines, through induced degradation of cytokine mRNA by the former and by inhibiting of NF- κ B-mediated transcription of cytokine genes by the later [19]. Another mechanism may involve Ca²⁺ and K⁺ channel blockers, e.g., toxins, which in abundant quantities are present in venoms of scorpions, belonging to *Leiurus* genus [2]. These channels are critically important for the activation of T-helpers, differentiation, and cytokine production [20]; thus, it is possible that specific toxins from LmV may inhibit the synthesis of pro-inflammatory cytokines, suppressing the immune response. Considering the fact that the balance between anti- and pro-inflammatory cytokines determines the degree and duration of the inflammation, it might be expected that LmV does not trigger the cytokine storm so the inflammation itself could not be prolonged due to the lack of pro-inflammatory cytokines, yet the important fact is that excessive and unequal anti-inflammatory response, as in our case, can lead to the insufficient neutralization of venom action [10], and therefore, to the potential tissue damage.

The results of HIF-1 α and NF- κ B contents determination could provide us the important information about the inflammation development on the level of transcription of the cytokine genes. These TFs play a key role in the intrarenal inflammation and AKI;

moreover it is already known that HIF-1 α expression is strongly regulated by NF- κ B [21]. HIF-1 α is overexpressed in hypoxia-related pathologies (such as inflammation), and it is responsible for facilitating the transcription of many genes, including pro-inflammatory ones [22]. NF- κ B is the central TF in the inflammatory response, being crucial for the expression of wide range of genes, especially cytokine genes [23]. In our study, envenomation led to the rapid increase in the HIF-1 α level and slightly less swift increase in NF- κ B level, suggesting about the significant immune response to the venom presence. At the same time, concentrations of pro-inflammatory cytokines in our experimental conditions were not increased (except for the IFN- γ), which may be associated with 2 phenomena, explained above. For example, the mechanism of IL-10 lies in the NF- κ B retention in the cytoplasm, instead of nucleus, therefore, the expression of pro-inflammatory genes can be insufficient even with increased levels of NF- κ B, which is unable to fulfill its direct functions outside of the nucleus [19].

GFs are substantial molecules in the homeostasis maintaining and recovery from the diseases. Their presence is usually associated with traumas, injuries or inflammation in general. Considering the fact that scorpion envenomation is inextricably connected with tissue damaging, relative GFs' levels can be indicative for the extent of damage, caused by the venom components, or by the inflammation mediators. EGF can be characterized as the best-known injury repairing cytokine, main function of which is to facilitate reepithelialization through the promotion of the cell migration and proliferation [24]. Moreover, in kidneys, this molecule is also responsible for controlling the Ca²⁺ and Na⁺ channels, and its elevated levels are connected with AKI and chronic kidney diseases [25]. FGF-2 is another GF, participating in the wound healing and tissue remodeling. In addition, FGF-2 can regulate the synthesis of ECM components [24], so the results of this study can be consistent with the MMP burst and likely extracellular matrix degradation, observable in various organs during *L. macroctenus* envenomation [8]. The activity of the VEGF is usually related to the angiogenesis, synthesis of this molecule is highly dependent on hypoxia, therefore, inflammation contributes to the elevated VEGF levels, mostly by HIF-1 α -dependent mechanism [26]. In this study, we have shown that the levels of FGF-2, EGF, and VEGF in the rats' kidneys rise in the response to the LmV. Moreover, taking into account the information mentioned above, we can conclude about the potential kidney damage, following the LmV injection. Kidneys, being responsible for the excretion of venom toxins and endotoxins, formed during envenomation, endure an extremely stressful conditions, so both toxins' actions and inflammation effects can expectedly lead to the violation of the kidneys integrity as well as to the impairments of the renal system overall. The consolidated summary of study's results is presented in Figure 3.

5. CONCLUSION

To sum up, we have shown that *L. macroctenus* envenomation can provide inflammation response in the rat's kidneys that can potentially lead to the renal impairment and other related diseases. Amidst the elevated concentrations of anti-inflammatory IL-10 and IL-4, only IFN- γ relative levels were increased, suggesting that envenomation leads to the substantial imbalance in pro- and anti-inflammatory cytokines levels during the immune response. At the same time,

significantly increased levels of TFs HIF-1 α and NF- κ B, and GFs EGF, FGF-2, and VEGF were observed, indicating the tissue hypoxia and potential kidneys damage, developing in the presence of venom toxins, endotoxins, and inflammation mediators. It is notable, that the peak levels of studied parameters were observed at 24 h of envenomation, strongly suggesting that this period is the most stressful for the renal system. This information can be implicated in the designing of treatment strategies of the *L. macroctenus* envenomation or be considered in the future studies of the LmV effects on the renal system.

6. AUTHORS' CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

7. FUNDING

There is no funding to report.

8. CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

9. ETHICAL APPROVALS

All experiments on animals were conducted according to the Guide for the Care and Use of Laboratory Animals (8th edition), and the experiments were approved by the Ethical Committee of Taras Shevchenko National University of Kyiv (protocol №2 approved August 19, 2021).

10. DATA AVAILABILITY

All the data is available with the authors and shall be provided upon request.

11. PUBLISHER'S NOTE

This journal remains neutral with regard to jurisdictional claims in published institutional affiliation.

REFERENCES

1. Fereidooni R, Shirzadi S, Ayatizadeh SH, Bahloul M, Tavangar A, Zomorodian SA, *et al.* Scorpion envenomation-associated myocarditis: A systematic review. *PLoS Negl Trop Dis* 2023;17:e0011219.
2. Amr ZS, Abu Baker MA, Al-Saraihe M, Warrell DA. Scorpions and scorpion sting envenoming (scorpionism) in the Arab countries of the middle East. *Toxicon* 2021;191:83-103.
3. Reis MB, Zoccal KF, Gardinassi LG, Faccioli LH. Scorpion envenomation and inflammation: Beyond neurotoxic effects. *Toxicon* 2019;167:174-9.
4. Roozbehani PM, Ghafourian M, Nemati M, Khosravi M, Salehi AM. Evaluation of pro-inflammatory and anti-inflammatory cytokine levels in rats treated with *Hottentotta saulcyi* scorpion venom. *Asia Pac J Med Toxicol* 2023;11:152-6.
5. Afify SM, Hassan G, Seno A, Seno M. Cancer-inducing niche: The force of chronic inflammation. *Br J Cancer* 2022;127:193-201.
6. Viswanathan S, Prabhu C. Scorpion sting nephropathy. *NDT Plus* 2011;4:376-82.
7. Gunas V, Maievskiy O, Raksha N, Vovk T, Savchuk O, Shchypanskyi S, *et al.* Protein and peptide profiles of rats' organs in scorpion envenomation. *Toxicol Rep* 2023;10:615-20.
8. Gunas V, Maievskiy O, Raksha N, Vovk T, Savchuk O, Shchypanskyi S, *et al.* The activity of metalloproteases and serine proteases in various organs after *Leiurus macroctenus* envenomation. *J Toxicol* 2023;2023:5262729.
9. Ozkan O, Filazi A. The determination of acute lethal dose-50 (LD50) levels of venom in mice, obtained by different methods from scorpions, *Androctonus crassicauda* (Oliver 1807). *Acta Parasitol Turc* 2004;28:50-3.
10. Petricevich VL. Scorpion venom and the inflammatory response. *Mediators Inflamm* 2010;2010:903295.
11. Petricevich VL. Balance between pro-and anti-inflammatory cytokines in mice treated with *Centruroides noxius* scorpion venom. *Mediators Inflamm* 2006;2006:54273.
12. Luzina IG, Keegan AD, Heller NM, Rook GA, Shea-Donohue T, Atamas SP. Regulation of inflammation by interleukin-4: A review of "alternatives". *J Leukoc Biol* 2012;92:753-64.
13. Zhang MZ, Wang X, Wang Y, Niu A, Wang S, Zou C, *et al.* IL-4/IL-13-mediated polarization of renal macrophages/dendritic cells to an M2a phenotype is essential for recovery from acute kidney injury. *Kidney Int* 2017;91:375-86.
14. Ip WK, Hoshi N, Shouval DS, Snapper S, Medzhitov R. Anti-inflammatory effect of IL-10 mediated by metabolic reprogramming of macrophages. *Science* 2017;356:513-9.
15. Makita N, Hizukuri Y, Yamashiro K, Murakawa M, Hayashi Y. IL-10 enhances the phenotype of M2 macrophages induced by IL-4 and confers the ability to increase eosinophil migration. *Int Immunol* 2015;27:131-41.
16. Azevedo E, Figueiredo RG, Pinto RV, Ramos TC, Sampaio GP, Bulhosa Santos RP, *et al.* Evaluation of systemic inflammatory response and lung injury induced by *Crotalus durissus cascavella* venom. *PLoS One* 2020;15:e0224584.
17. Costal-Oliveira F, Guerra-Duarte C, Castro KL, Tintaya B, Bonilla C, Silva W, *et al.* Serological, biochemical and enzymatic alterations in rodents after experimental envenomation with *Hadruroides lunatus* scorpion venom. *Toxicon* 2015;103:129-34.
18. Bahloul M, Regaieg K, Chabchoub I, Kammoun M, Chtara K, Bouaziz M. Severe scorpion envenomations: pathophysiology and role of inflammation in multivisceral failure. *Med Sante Trop* 2017;27:214-21.
19. Van Meergeren ME, Roosendaal G, Jansen NW, Wenting MJ, van Wesel AC, van Roon JA, *et al.* IL-4 alone and in combination with IL-10 protects against blood-induced cartilage damage. *Osteoarthritis Cartilage* 2012;20:764-72.
20. Ryan RY, Seymour J, Loukas A, Lopez JA, Ikonopoulou MP, Miles JJ. Immunological responses to envenomation. *Front Immunol* 2021;12:661082.
21. Liu Z, Dong Z. A cross talk between HIF and NF- κ B in AKI. *Am J Physiol Renal Physiol* 2021;321:F255-6.
22. Palazon A, Goldrath AW, Nizet V, Johnson RS. HIF transcription factors, inflammation, and immunity. *Immunity* 2014;41:518-28.
23. Baker RG, Hayden MS, Ghosh S. NF- κ B, inflammation, and metabolic disease. *Cell Metab* 2011;13:11-22.
24. Barrientos S, Stojadinovic O, Golinko MS, Brem H, Tomic-Canic M. Growth factors and cytokines in wound healing. *Wound Repair Regen* 2008;16:585-601.
25. Staruschenko A, Palygin O, Ilatovskaya DV, Pavlov TS. Epidermal

- growth factors in the kidney and relationship to hypertension. *Am J Physiol Renal Physiol* 2013;305:F12-20.
26. Ramakrishnan S, Anand V, Roy S. Vascular endothelial growth factor signaling in hypoxia and inflammation. *J Neuroimmune Pharmacol* 2014;9:142-60.

How to cite this article:

Matkivska R, Shchypanskyi S, Raksha N, Vovk T, Halenova T, Maievskyi O, Savchuk O, Ostapchenko L. Cytokine disbalance in the rats' kidneys following *Leiurus macroctenus* envenomation. *J App Biol Biotech.* 2024;12(3):110-115. DOI: 10.7324/JABB.2024.163558