РЕЗУЛЬТАТЫ ЭКСПЕРИМЕНТАЛЬНОГО ПРИМЕНЕНИЯ МИКРОВЕЗИКУЛ МЕЗЕНХИМАЛЬНЫХ СТВОЛОВЫХ КЛЕТОК НА МОДЕЛИ ОСТРОЙ ПОЧЕЧНОЙ НЕДОСТАТОЧНОСТИ У МЫШЕЙ

Иванова И.П.[1], Селедцова Г.В.[1], Селедцов В.И.[2], Хабалова Т.С.[1], Доржиева А.Б.[1]

[1] ФГБНУ «Научно-исследовательский институт фундаментальной и клинической иммунологии», г. Новосибирск, Россия
[2] ФГБНУ «Российский научный центр хирургии имени академика Б.В. Петровского», Москва, Россия

Резюме. Важную роль в восстановлении поврежденных органов и тканей играют мезенхимальные стволовые клетки (МСК) и продуцируемые ими микровезикулярные частицы (МВ). Они могут быть источником цитокинов, антиапоптозных и стимуляторных ростовых факторов. Кроме того, МВ осуществляют транспорт мРНК, микроРНК и сигнальных белков в поврежденные ткани. Это повышает способность клеток к регенерации, ингибирует апоптоз, способствует ангиогенезу и стимулирует пролиферацию клеток. Целью исследования было изучение иммунорегулирующих и прорегенераторных свойств микровезикул мезенхимальных стволовых клеток (МСК-МВ) на модели глицерол-индуцированной острой почечной недостаточности (ОПН) у мышей. Эксперименты проводились на мышах линии СВА возрастом 3-4 месяца. ОПН индуцировали однократным внутримышечным введением 50% глицерола. МСК получали из костного мозга здоровых животных, культивировали в стандартных условиях. Микровезикулы получали путем центрифугирования при 12000 g супернатанта МСК после индукции их апоптоза путем культивирования в условиях депривации кислорода и в бессывороточной среде. МСК-МВ вводили внутривенно в ретроорбитальный синус через сутки после индукции ОПН. Дозу МВ рассчитывали как эквивалентную (полученную из) 1 млн МСК, что составляло 100 мкл на мышь. Животных выводили из эксперимента на 4-е и 11-е сутки после инъекции МСК-МВ. Забирали плазму крови для определения уровня креатининна, мочу – для анализа альбумина, почки – для гистологического иссследования. Показано, что МВ, подуцируемые МСК,

Адрес для переписки:

Иванова Ирина Петровна
ФГБНУ «Научно-исследовательский институт фундаментальной и клинической иммунологии»
630099, Россия, г. Новосибирск, ул. Ядринцевская, 14.
Тел.: 8 (913) 746-41-98.
Факс: 8 (383) 222-48-61.
E-mail: irinaiki@rambler.ru

Address for correspondence:

Irina P. Ivanova
Research Institute of Fundamental and Clinical Immunology
14 Yadrinzevskaya St
Novosibirsk
630099 Russian Federation
Phone: +7 (913) 746-41-98.
Fax: +7 (383) 222-48-61.
E-mail: irinaiki@rambler.ru

Образец цитирования:

И.П. Иванова, Г.В. Селедцова, В.И. Селедцов, Т.С. Хабалова, А.Б. Доржиева «Результаты экспериментального применения микровезикул мезенхимальных стволовых клеток на модели острой почечной недостаточности у мышей» // Медицинская иммунология, 2023. Т. 25, № 3. С. 665-672.
doi: 10.15789/1563-0625-EAR-2716

For citation:

I.P. Ivanova, G.V. Seledtsova, V.I. Seledtsov, T.S. Khabalova, A.B. Dorzhieva "Experimental application results of mesenchymal stem cell microvesicles in the mouse model of acute renal failure", Medical Immunology (Russia)/ Meditsinskaya Immunologiya, 2023, Vol. 25, no. 3, pp. 665-672.
doi: 10.15789/1563-0625-EAR-2716

DOI: 10.15789/1563-0625-EAR-2716

дозозависимо стимулировали пролиферацию спленоцитов как в спонтанном, так и Кон-А индуцированном тесте. Добавление МВ вызывало снижение доксорубицин-индуцированного апоптоза селезеночных лимфоцитов у мышей. Вероятно, в этом случае, продуцируемые МСК-МВ оказывали иммуностимулирующее и антиапоптотическое действие. Также МВ оказывали положительный эффект на восстановление структуры и функции почек в модели острой почечной недостаточности у мышей. Использование МСК-МВ в лечении ОПН, индуцированной однократным введением 50% глицерола способствовало снижению уровня альбумина в моче и восстановлению уровня креатинина в сыворотке крови животных. Морфологические исследования показали уменьшение высоты клеток и диаметра собирательных трубочек в мозговом веществе и уменьшение наибольшего поперечного диаметра суперфициальных клубочков в корковом веществе почек больных мышей. Таким образом, полученные результаты свидетельствуют о значительных терапевтических и прорегенеративных свойствах МСК-МВ, которые требуют дальнейшего изучения.

Ключевые слова: мезенхимальные стволовые клетки, микровезикулы, терапевтическое применение микровезикул, регенерация, острая почечная недостаточность, болезни почек

EXPERIMENTAL APPLICATION RESULTS OF MESENCHYMAL STEM CELL MICROVESICLES IN THE MOUSE MODEL OF ACUTE RENAL FAILURE

Ivanova I.P.[a], Seledtsova G.V.[a], Seledtsov V.I.[b], Khabalova T.S.[a], Dorzhieva A.B.[a]

[a] *Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russian Federation*
[b] *B. Petrovsky Russian Scientific Center for Surgery, Moscow, Russian Federation*

Abstract. An important role in restoration of damaged organs and tissues is played by mesenchymal stem cells (MSCs) and microvesicular particles (MV) produced by them. They can be a source of cytokines, anti-apoptotic and growth stimulating factors. In addition, MVs carry out transport of mRNA, miRNA, and signal proteins into damaged tissues. This increases the ability of cells to regenerate and to inhibit apoptosis, promote to angiogenesis and stimulate cell proliferation. The aim of our research was to study the immunoregulatory and pro-regenerative properties of mesenchymal stem cell microvesicles (MSC-MV) in a model of glycerol-induced acute renal failure (ARF) in mice. The experiments were carried out on CBA mice aged 3-4 months. AKI was induced by a single intramuscular injection of 50% glycerol. MSCs were obtained from the bone marrow of healthy animals and cultivated under standard conditions. Microvesicles were obtained by centrifugation at 12000g of MSC supernatant after induction of their apoptosis by culturing under oxygen deprivation conditions and in serum-free medium. MSC-MV was injected intravenously into the retroorbital sinus one day after induction of ARF. The MV dose was calculated as equivalent to (derived from) 1 million MSCs, which was 100 μL per mouse. Animals were taken out of the experiment on days 4 and 11 after MSC-MV injection. Blood plasma was taken to determine the level of creatinine, urine – for albumin analysis, kidneys – for histological examination. It has been shown that MVs induced by MSCs dose-dependently stimulated splenocyte proliferation in both spontaneous and Con-A induced tests. The addition of MV caused a decrease in doxorubicin-induced apoptosis of splenic lymphocytes in mice. Probably, in this case, MV produced by MSCs had an immunostimulatory and antiapoptotic effect. Also, MVs had a positive impact on the restoration of structure and function kidneys in a model of ARF in mice. The use of MSC-MV in treatment of acute renal failure induced by a single injection of 50% glycerol contributed to decrease albumin level urine and restoration of creatinine level in blood serum of animals. Morphological studies have shown decrease in the height cell and collecting duct diameter in the medulla and a decrease in the largest transverse diameter of superficial glomeruli in the renal cortex of sick mice. Thus, the obtained results indicate significant therapeutic and pro-regenerative properties of MSC-MV, which require further study.

Keywords: mesenchymal stem cells, microvesicles, therapeutic use of microvesicles, regeneration, acute renal failure, kidney disease

Introduction

Increasing evidence indicates important role of mesenchymal stem cells (MSCs) in restoration damaged organs and tissues. Their cytoprotective effect is due not only for processes homing and differentiation, but also stimulation endogenous regeneration resident cells [8]. This occurs due to cytokines secretion, anti-apoptotic and growth factors, production of microvesicular particles (exosomes and microvesicles) (MSC-MV), which purposefully deliver mRNA, microRNA, and signal proteins for damaged tissues [3, 5].

A number of experimental studies have shown introduction of microvesicular particles (MV) largely repeats therapeutic effect of MSCs in various experimental models of tissue damage, for example, in acute damage of tubular epithelium induced by intramuscular glycerol administration or acute ischemia-reperfusion [2, 5, 6, 10]. Thus, in a model with glycerol-induced acute renal failure (ARF), it was shown that MVs carry on their surface CD29, CD44, CD73, specific markers of MSCs, which provide targeted MVs transport to the injury site. It was also shown that MSC-MVs carry out horizontal transport of mRNA MSCs and involve in control of transcription, proliferation, and immunoregulation. Once in the lesion, MV inhibit apoptosis and stimulate proliferation of tubular epithelial cells, thus significantly to reduce manifestations ARF in laboratory animals [2]. Similar results were obtained in experimental model kidney ischemia-reperfusion, where it was also shown that MV reduce manifestations postischemic nephrosclerosis and developing chronic renal failure [6]. In our study, we analyzed the effects of exposure MVs derived from MSCs on changes in immunological, biochemical, and morphological parameters during glycerol-induced acute renal failure in mice.

Materials and methods

The experiments were carried out on linear CBA mice aged 3-4 months. Acute renal failure was induced by single intramuscular injection of 50% glycerol at a dose of 8.6 mg/kg. Resulting rhabdomyolysis has mixed (ischemic, toxic, retention) effect on kidneys. In preliminary experiments, we showed that such an impact causes acute necrosis of proximal renal tubules epithelial cells accompanied by a rather significant increase in the level of blood serum urea. All experiments on animals were carried out in accordance with the "Rules for carrying out work using experimental animals" (Appendix to the order of the Ministry of Health of the USSR No. 755 of 1977).

Mesenchymal stromal cells were obtained from bone marrow syngeneic mice by the method of adhesion to cultural plastic. Bone marrow derived from femurs and tibias was suspended in RPMI with 10% FCS. Bone marrow stroma was mechanically destroyed with a glass homogenizer, washed twice, and placed in culture dishes in complete medium based on RPMI 1640. Non-adherent fraction of bone marrow cells was removed at culture medium changes starting from day 3. MSCs had classic fibroblast-like phenotype and formed a continuous monolayer by 4th week of cultivation. MSCs were removed from plastic with 0.25% versene-trypsin solution, after which cells were washed twice from culture medium and resuspended in physiological saline.

After reaching monolayer, 1×10^6/mL of MSCs were subjected to apoptosis by culturing under oxygen deprivation conditions and in a serum-free medium for 1-3 days (the culture flask was placed in container, a candle was lit nearby, and the lid was hermetically closed). Under these conditions, cells enter state of apoptosis, and their production of microvesicular particles, especially fractions of 100-1000 nm, increases significantly. At the end of cultivation, 1 million cells were centrifuged at 2000 g for 15 minutes to remove cell debris. The supernatant was additionally centrifuged at 12000 g for 60 minutes at 4 °C. The resulting pellet was resuspended in 100 μL of saline. Thus, standard for the amount of MV was their preparation from 1 million cells and dilution in 100 μL of 0.9% NaCl solution. In some experiments, protein content was determined in the obtained MVs by the Bradford method, and MV size was estimated by cytofluorimetry. The MV size was 100 nm-1000 nm, which was confirmed by cytofluorimetry using the FACS-CytoFLEX instrument.

MV was administered intravenously into the mouse retroorbital sinus one day after induction of acute renal failure. The MV dose was calculated as equivalent to 1 million MSCs, which was 100 μL per mouse. Animals with induced acute renal failure were withdrawn from the experiment on days 4 and 11 after MV injection. Blood plasma was collected to determine level of creatinine, urine – for albumin analysis, kidneys for histological examination, splenocytes for evaluation of proliferation and cell cycle.

Effect of microvesicular particles on splenocyte proliferation was studied in the 3H-thymidine incorporation test. Splenocytes were obtained by homogenizing the syngeneic mice spleens and then cultured in a 96-well plate at 300,000 cells per well in complete medium with or without addition MV for 3 days. The dose MV was calculated from the protein by Bradford method and added at 10 μg/mL, 30 μg/mL and 90 μg/mL. H3-thymidine was added 16 hours before finish culture. The results were evaluated on β-scintillation counter.

Splenocytes from CBA mice were cultured 2 days in a 6-well plate at 5 million cells per well in complete medium in absence or presence of microvesicles at 90 μg/mL for determine effect microvesicular particles

on resistance lymphocytes for apoptosis. Then, for induce apoptosis, doxorubicin was added at a dose of 0.1 μmol/l for a period of 24 hours. Next, cells were removed, fixed with 0.5% paraformaldehyde, stained with propidium iodide. The percentage of cells in the state of apoptosis was evaluated on a FACSCalibur flow cytometer. Splenocytes from healthy mice and splenocytes from mice with glycerol-induced renal failure were used in the experiment. Serum creatinine was measured using BioVision, Creatinine (Mouse) ELISA Kit rev 03/18, Catalog Number E4369-100 (Abcam); urinary albumin was measured using Mouse Albumin ELISA Kit, Catalog Number ab108792 (Abcam).

For histological examination mice kidneys were fixed in 4% formalin solution, then dehydrated according to standard procedure and embedded in paraffin. Paraffin sections 4-5 μm thick were obtained using a rotary microtome HM 340E (Carl Zeiss, Germany), stained with hematoxylin and eosin, Sirius red and Mallory. Light-optical examination and microphotography were carried out using an Axioskop 40 microscope (Carl Zeiss, Germany). Morphometric analysis of kidney structures was performed on paraffin sections. The values of the following morphometric parameters were determined: – diameters superficial renal glomeruli (renal corpuscles); diameters collecting ducts and height their cells, measured in the middle third renal medulla. Morphometric calculation was performed in a field of view with an eyepiece 10×/25 and a lens 63×. The data obtained during the study were processed using the one-way ANOVA method. Values were calculated using GraphPad Prism 8 software. The results were analyzed using the computer program Graph prism 8. Student's T-test was used to assess the significance of differences.

Results and discussion

Figure 1 shows the results splenocyte proliferation and their apoptosis levels after MSC-MV exposure. We found a significant dose-dependent stimulatory activity of MSC-MV in both spontaneous and Con-A induced proliferative tests. The proliferative activity of splenocytes increased 3-fold after addition of 10 μg/mL MSC-MV, cultivation in presence of 30 and 90 μg/mL MSC-MV had an even more pronounced effect (Figure 1A, B). Also, MV addition caused decrease level of splenocyte apoptosis (Figure 1C). Thus, microvesicles produced by MSCs had an immunostimulatory effect and showed a high potential in maintaining and stimulating cell growth.

Mice were induced with ARF. Three experimental groups were formed for the study: intact animals; mice with ARF; mice with ARF treated with MSC-MV. Functional and biochemical parameters of excretory system and morphological changes in structure kidneys were studied in this groups on days 4 and 11 after intravenous administration of MSC-MV. After intramuscular injection of 50% glycerol on day 4 the level of urine albumin increased 3 times in experimental group mice compared with intact animals. MSC-MV introduction led to decrease in albumin (Table 1). The blood serum creatinine concentration mice with acute renal failure on day 4 did not differ from the values of intact mice, only on day 11 we recorded a significant increase in this indicator by 1.5 times. The MSC-MV restored the level of creatinine to control values in these experiments (Table 1). Thus, MVs had a positive effect on restoration of glomerular apparatus and excretory function of kidneys.

According to the results of morphological analysis, it can be said that in the group of mice with induced ARF on 4th day studies was enlarged (compared to intact group) superficial glomeruli are detected in the renal cortex. Cell height and collecting duct diameter was increased in the medulla (Figure 2A). Blood rheological properties in the papillae kidney manifested in the form of plasma proteins sweating and erythrocyte sludge. The urinary space of the glomeruli of cortical substance is practically not determined in the group ARF study kidney on 11th day. It was probably caused by reduced an amount

TABLE 1. BIOCHEMICAL PARAMETERS IN URINE AND BLOOD SERUM OF MICE WITH ACUTE RENAL FAILURE ON DAYS 4 AND 11 AFTER EXPOSURE TO MSC MICROVESICLES.

Albumin concentration (ng/mL) in mice urine			
	Intact	**ARF**	**ARF + MSC-MV**
4th day	98.41±15.63	298.61±51.55	172.60±74.39
11th day		243.42±19.72	132.10±38.22
Creatinine concentration (ng/mL) in mice blood			
	Intact	**ARF**	**MSC+ MSC-MV**
4th day	2.24±0.16	2.379±0.090	2.65±0.12
11th day		3.114±0.390	1.91±0.12*

Note. * $p < 0.05$, significance of differences in comparison with the ARF group.

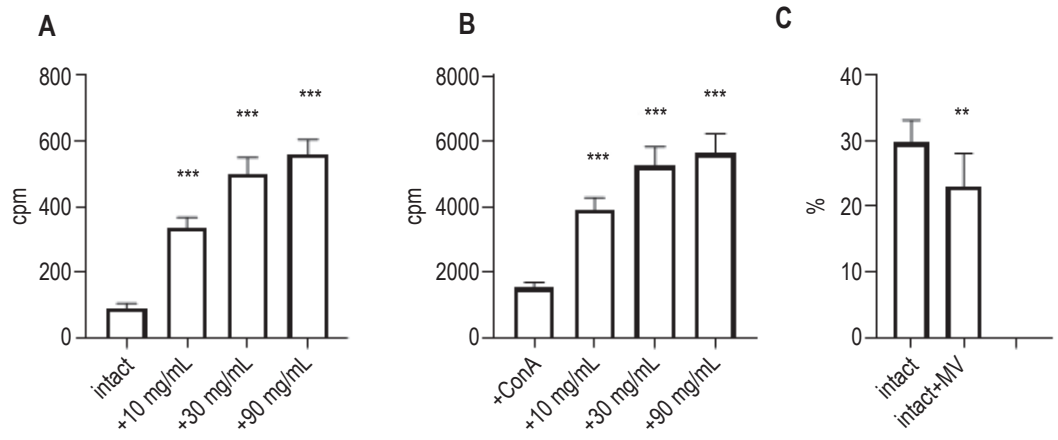

Figure 1. Proliferative response (A – in absence or B – in presence of Kon A) and splenocyte apoptosis (C) of mice in response to MSC-MV exposure

Note. 10 μg/mL, 30 μg/mL, 90 μg/mL, MV concentration in culture liquid. ** p < 0.01; *** p < 0.001, significance of differences compared to lymphocytes without addition of MV.

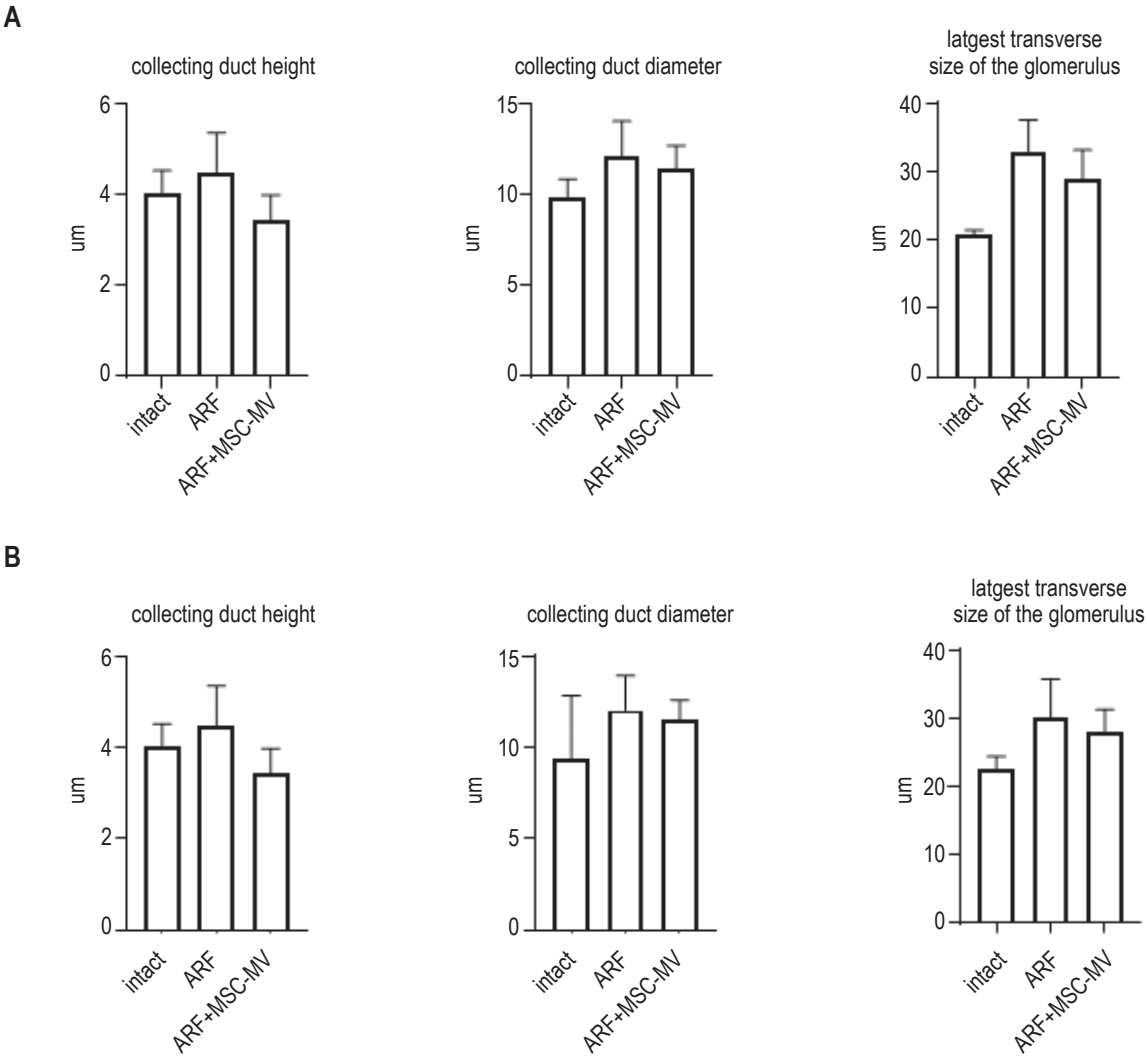

Figure 2. Morphological changes of kidney structure in acute renal failure on day 4 (A) and day 11 (B) of the study

of filtered urine. There is a sharp degeneration of glomerular cells (the size of the mesangial cells, the intercellular substance is reduced), the transverse size of glomeruli themselves is increased (micrographs of morphological data are not presented).

Morphological kidney changes were less pronounced in the group of mice with injected MSC-MV compared to the group ARF mice on research day 4. The height cells and collecting duct diameter are reduced in renal medulla, while we recorded increase the Henle loops lumen and decrease degeneration of the Henle loops cells. There is also insignificant decrease in the largest transverse diameter superficial glomeruli (Figure 2A). Partial spontaneous restoration structure kidneys occurred on the research 11th day, however, the MSC-MV introduction accelerates this process. There are minimal changes in the size glomeruli kidneys, no dystrophic changes were registered in the cortex (Figure 2B). Thus, in the model ARF, pronounced regenerative effect of microvesicles obtained from MSCs is noted. This effect was confirmed both morphologically and functionally by determining of albumin level in urine and creatinine in blood serum.

Microvesicles have structures 100-1000 nm. Their membrane separates from cytoplasmic membrane cells and carries various enzymes, transcription factors, mRNA molecules. MV formation is characteristic for many types of cells – leukocytes, erythrocytes, stem and tumor cells. At present, their participation in development of many cardiovascular and neurological diseases, invasion and metastasis tumor cells has been established [12]. The importance of extracellular vesicles lies in their ability to transfer biologically active molecules and genetic information to other target cells, influencing their functions [3]. Stem cell-derived MVs promote tissue repair and reduce inflammation in various models of ARF [4].

The hallmark of ARF is a rapid decline in kidney function in parallel with loss of tubular cells, leading to an increase in urea and creatinine plasma. MSC-MVs from a bone marrow accelerate to repair of damaged tubular cells, promoting cell proliferation and protecting cells from apoptosis [2]. The effects of MV are mainly associated with horizontal transfer of genetic material [5]. For example, MSC-MV from a bone marrow carry specific mRNAs that to stimulate damaged recipient cells to re-enter a cell cycle [2]. There is also evidence that transfer of human IGF-1 receptor mRNA (present in bone marrow MSC-MV) to tubular cells is a fundamental event to initiate kidney recovery [13]. In models of toxic acute renal failure induced by cisplatin and gentamicin, MSC-MV improved kidney function and reduced classical histological signs of the disease [15]. Similar results were obtained using umbilical cord blood MSC-MV, human liver stem cells, which showed high clinical efficacy in experimental conditions of acute renal failure.

Conclusion

In our work, we found MVs derived from MSCs are able to enhance proliferation splenocytes and reduce level of their apoptosis in an experimentally induced system. Also, on the ARF model, we recorded an improvement in excretory function of kidneys, assessed by normalization of biochemical parameters in urine and blood (albumin, creatinine) and restoration of morphological structure already on the 4th day after introduction of MSC-MV. At the same time, MSCs have immunoregulatory properties [9]. Immune system contribution in processes damage and restoration renal tissue has been shown in a number of works. In acute kidney injury, regardless of genesis, there is an increased activity of many its components, an enhancement in local production of cytokines number, growth and colony-stimulating factors [7, 11]. There are also data on a negative role of T, B lymphocytes and activated macrophages in the pathogenesis of renal failure. [11, 14]. At the same time, T regulatory cells number increasing contributes anti-inflammatory effect [1, 11]. Considering the above, we believe it appropriate to further study immunoregulatory properties not only MSCs, but also microvesicles produced by them.

Acknowledgments

We express our gratitude for pathomorphology assessment of samples to PhD Prokopieva Elena Alexandrovna, Geletina Nadezda Sergeevna; to Belogorodtsev Sergey Nikolaevich for help with models.

References

1. Alikhan M.A., Huynh M., Kitching A.R., Ooi J.D. Regulatory Tcells in renal diseases. *Clin. Transl. Immunol., 2018, Vol. 7, no. 1, 1004.* doi: 10.1002/cti2.1004.
2. Bruno S., Grange C., Deregibus M.C., Calogero R.A., Savozzi F.C., Morando L., Busca A., Falda M., Bussolati B., Tetta C., Camussi G. Mesenchymal stem cell-derived microvesicles protect against acute tubular injury. *J. Am. Soc. Nephrol., 2009, Vol. 20, no. 5, pp. 1053-1067.*
3. Camussi G., Deregibus M.C., Bruno S., Cantaluppi V., Biancone L. Exosomes/microvesicles as a mechanism of cell-to-cell communication. *Kidney Int., 2010, Vol. 78, no. 9, pp. 838-848.*
4. Cantaluppi V., Biancone L., Quercia A., Deregibus M.C., Segoloni G., Camussi G. Rationale of mesenchymal stem cell therapy in kidney injury. *Am. J. Kidney Dis., 2013, Vol. 61, no. 2, pp. 300-309.*

5. Deregibus M.C., Cantaluppi V., Calogero R., Lo Iacono M., Tetta C., Biancone L., Bruno S., Bussolati B., Camussi, G. Endothelial progenitor cell derived microvesicles activate an angiogenic program in endothelial cells by a horizontal transfer of mRNA. *Blood, 2007, Vol. 110, no. 7, pp. 2440-2448.*

6. Gatti S., Bruno S., Deregibus M.C., Sordi A., Cantaluppi V., Tetta C., Camussi G. Microvesicles derived from human adult mesenchymal stem cells protect against ischaemia-reperfusion-induced acute and chronic kidney injury. *Nephrol. Dial. Transplant., 2011, Vol. 26, no. 5, pp. 1474-1483.*

7. Goes N., Urmson J., Ramassar V., Halloran P.F. Ischemic acute tubular necrosis induces an extensive local cytokine response: evidence for induction of interferon-gamma, transforming growth factor-1, granulocyte-macrophage colony-stimulating factor, interleukin-2, and interleukin-10. *Transplantation, 1995, Vol. 59, no. 4, pp. 565-572.*

8. Humphreys B.D., Valerius M.T., Kobayashi A., Mugford J.W., Soeung S., Duffield J.S., McMahon A.P., Bonventre J.V. Intrinsic epithelial cells repair the kidney after injury. *Cell Stem Cell, 2008, Vol. 2, no. 3, pp. 284-291.*

9. Nauta A.J., Fibbe W.E. Immunomodulatory properties of mesenchymal stromal sells. *Blood, 2007, Vol. 110, no. 10, pp. 3499-3506.*

10. Quesenberry P.J., Dooner M.S., Aliotta J.M. Stem cell plasticity revisited: the continuum marrow model and phenotypic changes mediated by microvesicles. *Exp. Hematol., 2010, Vol. 38, no. 7, pp. 581-592.*

11. Rabb H. Immune modulation of acute kidney injury. *J. Am. Soc. Nephrol., 2006, Vol. 17, no. 3, pp. 604-606.*

12. Stahl A., Johanson K., Mossberg M., Kahn R., Karpman D. Exosomes and microvesicules in normal physiology, pathophysiology and renal deseases. *Pediatr. Nephrol., 2019, Vol. 34, no. 1, pp. 11-30.*

13. Wang S.Y., Hong Q., Zhang C.Y., Yang Y.J., Cai G.Y., Chen X.M. miRNAs in stem cell-derived extracellular vesicles for acute kidney injury treatment: comprehensive review of preclinical studies. *Stem Cell Res. Ther., 2019, Vol.10, no. 1, 281.* doi: 10.1186/s13287-019-1371-1.

14. Wang Y., Wang Y., Cao Q., Zheng G., Lee V.W.S., Zheng D., Li X., Tan T.K., Harris D.C.H. By homing to the kidney, activated macrophages potently exacerbate renal injury. *Am. J. Pathol., 2008, Vol. 172, no. 6, pp. 1491-1499.*

15. Zhou Y., Xu H., Xu W., Wang B., Wu H., Tao Y., Zhang B., Wang M., Mao F., Yan Y., Gao S., Gu H., Zhu W., Qian H. Exosomes released by human umbilical cord mesenchymal stem cells protect against cisplatin-induced renal oxidative stress and apoptosis *in vivo* and *in vitro*. *Stem Cell Res. Ther., 2013, Vol. 4, no. 2, 34.* doi: 10.1186/scrt194.

Авторы:

Иванова И.П. *— к.м.н., старший научный сотрудник лаборатории клинической иммунопатологии ФГБНУ «Научно-исследовательский институт фундаментальной и клинической иммунологии», г. Новосибирск, Россия*

Селедцова Г.В. *— д.м.н., главный научный сотрудник лаборатории клинической иммунопатологии ФГБНУ «Научно-исследовательский институт фундаментальной и клинической иммунологии», г. Новосибирск, Россия*

Authors:

Ivanova I.P., *PhD (Medicine), Senior Research Associate, Laboratory of Clinical Immunopathology, Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russian Federation*

Seledtsova G.V., *PhD, MD (Medicine), Chief Research Associate, Laboratory of Clinical Immunopathology, Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russian Federation*

Селедцов В.И. *– д.м.н., профессор, главный научный сотрудник ФГБНУ «Российский научный центр хирургии имени академика Б.В. Петровского», Москва, Россия*

Seledtsov V.I., *PhD, MD (Medicine), Professor, Chief Research Associate, B. Petrovsky Russian Scientific Center for Surgery, Moscow, Russian Federation*

Хабалова Т.С. *– младший научный сотрудник лаборатории клинической иммунопатологии ФГБНУ «Научно-исследовательский институт фундаментальной и клинической иммунологии», г. Новосибирск, Россия*

Khabalova T.S., *Reseach Associate, Laboratory of Clinical Immunopathology, Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russian Federation*

Доржиева А.Б. *– аспирант ФГБНУ «Научно-исследовательский институт фундаментальной и клинической иммунологии», г. Новосибирск, Россия*

Dorzhieva A.B., *Postgraduate Student, Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russian Federation*

Поступила 12.04.2023
Принята к печати 26.04.2023

Received 12.04.2023
Accepted 26.04.2023