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Intrastromal implantation of track-etchedmembranes overlaid by prenatal stromal cells for bullous keratopathy in the experiment

Filippova E.O.[1, 2], Krivosheina O.I.[2], Khlusov I.A.[1, 2, 3], Pichugin V.F.[1], Dzyuman A.N.[2], Zaitsev K.V.[3]

[1] *National Research Tomsk Polytechnic University (NR TPU)*
30, Lenina Ave., Tomsk, 634050, Russian Federation

[2] *Siberian State Medical University (SSMU)*
2, Moscow Trakt, Tomsk, 634050, Russian Federation

[3] *Federal Siberian Research Clinical Center FMBA of Russia*
4, Mira Str., Seversk, 636035, Russian Federation

ABSTRACT

The aim of the research is to study the possibility of using track-etched membrane, including track-etched membranes modified with cold plasma, followed by layering prenatal stem cells (PSC) on the material surface in surgical treatment of bullous keratopathy (BK).

Materials and methods. The track membranes made of polyethylene terephthalate were obtained by irradiating the polymeric film with the $^{40}Ar^{+8}$ ion beams and by chemical etching. The study was conducted on 16 rabbits (Sylvilagus bachmani), which after BK modelling were divided into 4 groups: the 1st group was a control group of 4 animals (4 eyes); the 2nd group was a group of 4 animals (4 eyes) into which were implanted TM; the 3rd group was a group of 4 animals (4 eyes) into which were implanted TM with PSC; the 4th group was a group of 4 animals (4 eyes) into which were implanted plasma modified TM with PSC. TM was obtained by irradiating the PET film with $^{40}Ar^{+8}$ ions and subsequent chemical etching. The eyes were enucleated for histological examination after 8 weeks from the start of the experiment.

Results. As a result of the research, it was found that the implantation of TM with a preliminary layering of human PSC promotes the growth of the fibroblast population in the cornea stroma and intensifies leukocyte (lymphocytes and eosinophilic granulocytes) infiltration as opposed to the implantation of PET TM without a cellular component. In addition, the implantation of TM contributes to a twofold decrease in the cornea edema induced by BK. Modification of TM with cold plasma did not affect the studied histomorphometric parameters. **Conclusion**. The implantation of TM based on PET during bullous keratopathy contributed to the development of the productive phase of infiltrative inflammation in the cornea of the eye. Pre-layering of human PSC reduced the severity of destructive changes in the rabbit cornea after BK modeling. The modification of TM by cold plasma did not affect the studied histomorphometric parameters.

Key words: cornea, bullous keratopathy, track etched-membranes, human stromal cells.

Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

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✉ *Хлусов Игорь Альбертович*, e-mail: khlusov63@mail.ru.

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Интрастромальная имплантация трековых мембран с пренатальными стромальными клетками человека при эндотелиально-эпителиальной дистрофии роговицы в эксперименте

Филиппова Е.О.[1, 2], Кривошеина О.И.[2], Хлусов И.А.[1, 2, 3], Пичугин В.Ф.[1], Дзюман А.Н.[2], Зайцев К.В.[3]

[1] *Национальный исследовательский Томский политехнический университет (НИ ТПУ)*
Россия, 634050, г. Томск, пр. Ленина, 30

[2] *Сибирский государственный медицинский университет (СибГМУ)*
Россия, 634050, г. Томск, Московский тракт, 2

[3] *Сибирский федеральный научно-клинический центр (СибФНКЦ) ФМБА России*
Россия, 636035, Томская область, г. Северск, ул. Мира, 4

РЕЗЮМЕ

Цель работы. Провести исследование применения трековых мембран (ТМ) на основе полиэтилентерефталата (ПЭТФ), в том числе модифицированных холодной плазмой с наслоением на их поверхность культуры пренатальных стромальных клеток (ПСК) человека в хирургическом лечении эндотелиально-эпителиальной дистрофии (ЭЭД) роговицы.

Материалы и методы. ТМ получали путем облучения ПЭТФ ионами $^{40}Ar^{+8}$ и химического травления. ЭЭД роговицы моделировали на 16 кроликах породы Sylvilagus bachmani, разделенных на четыре группы. Группа 1 – ЭЭД роговицы без лечения; группа 2 – ЭЭД с имплантацией в собственное вещество роговицы немодифицированной плазмой ТМ; группа 3 – ЭЭД с имплантацией в роговицу немодифицированной плазмой ТМ и наслоенной культурой ПСК человека; группа 4 – ЭЭД с имплантацией модифицированной плазмой ТМ и наслоенной культурой ПСК человека. Спустя 8 нед от начала эксперимента производили гистологическое исследование роговицы кроликов.

Основные результаты. Имплантация ТМ в строму роговицы при ЭЭД роговой оболочки способствует уменьшению (в 1,5 раза) отека ее собственного вещества и более интенсивному (в 1,7 раза) накоплению фибробластов вблизи ТМ по сравнению с состоянием роговицы в группе модели заболевания без лечения. Наличие ПСК человека на поверхности ТМ независимо от исходного состояния полимерного материала после интрастромальной имплантации индуцирует пролиферацию фибробластов в 1,5–1,8 раз и неоваскуляризацию стромы роговицы в 1,8–2,0 раза по сравнению с имплантацией ТМ без культуры клеток. Степень гидратации собственного вещества роговой оболочки при этом уменьшается в 1,3–1,5 раза. Модификация ТМ холодной плазмой не оказывает влияния на изученные морфометрические показатели роговицы.

Заключение. Имплантация ТМ из ПЭТФ при ЭЭД способствует развитию продуктивной фазы инфильтративного воспаления в роговице глаза кроликов. Предварительная *in vitro* адгезия ПСК человека на ТМ уменьшает выраженность деструктивных изменений роговицы кролика после моделирования ЭЭД. Модификация ТМ холодной плазмой не влияет на изученные морфометрические показатели роговицы.

Ключевые слова: роговица, эндотелиально-эпителиальная дистрофия, трековые мембраны, прена-

тальные стромальные клетки человека.

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INTRODUCTION

Bullous keratopathy (BK) is one of the leading causes of a chronic corneal edema and visual loss among corneal diseases. The main reason for bullous keratopathy development is the loss of pump function and/or barrier function in the corneal endothelium. There are different methods of bullous keratopathy treatment such as surgical methods and drugs, however, they do not always provide high and stable clinical and functional results. One of the promising treatments of BK is the use of permeable membranes which can normalize the fluid movement in the cornea and ensure its transparency [1–3]. Therefore, the search for and creation of biocompatible materials capable of maintaining the cornea in a weakly dehydrated state is a topical task. A track-etched membrane (TM) based on polyethylene terephthalate polymer (PET) is attractive material for bullous keratopathy treatment. In addition, the layering of stem cells on the material surface can stabilize the pathological process and significantly increase regeneration.

However, the amount of the surface energy of the TM based on PET is fairly low (~32 MJ/m2) [4]. It results in the fact that surface properties of the material, such as hydrophilicity, do not always meet the requirements, which is critical for using the membrane as a corneal implant and for cells adhesion. The exposure to low-temperature plasma is one of the most promising and innovative methods of modifying the surface of polymer materials. The advantage of the exposure to plasma is low penetration depth of its particles into the material and the change of properties only in the surface layer of the material, without any significant heat input [5]. In addition, according to studies [6],plasma modification of polymeric materials increases the wettability of materials and the adhesion of fibroblasts, does not affect cell proliferation and makes this type of modification more attractive for cell cultivation on artificial thin films.

The aim of the research was to study the possibility of using track-etched membranes, including track-etched membranes modified with cold plasma, followed by layering prenatal stem cells on the material surface in surgical treatment of bullous keratopathy.

MATERIALS AND METHODS

The track membranes made of polyethylene terephthalate were obtained by irradiating the polymeric film with the $^{40}Ar^{+8}$ ion beams and by the chemical etching. The modification of the track membranes surface was conducted using the atmospheric low-temperature plasma experimental device, based on the charge barrier (Tomsk Polytechnic University). The time of plasma exposure on the surface of each membrane comprised 30 seconds. TM was sterilized by gamma radiation of the radionuclide ^{60}Co with the dosages of 1 kGy (Si).

The *in vivo* study of TM biocompatibility was carried out on 16 *Sylvilagus bachmani* rabbits weighing 3.5–4.0 kg. Each animal under the operating conditions was modelled with BK by mechanical damage and removal of the corneal endothelium as described previously. The rabbits were divided into 4 groups 2 weeks after the development of the pathological process in the cornea: the 1st group was a control group of 4 animals (4 eyes); the 2nd group was a group of 4 animals (4 eyes) into which were implanted TM;

the 3rd group was a group of 4 animals (4 eyes) into which were implanted TM with cells; the 4th group was a group of 4 animals (4 eyes) into which were implanted plasma modified TM with cells.

The prenatal stromal cells (PSC) culture originally isolated from the light 11-week human embryo maintained ex vivo (line FL-42, Stem cell bank, Tomsk) was layered on TM. TM (samples with the linear size of 10 Ч 10 mm^2 and the length of up to 10 μm) was put in 24-well culture plates (Orange Scientific, Belgium) into which cell suspension was added at a concentration of 3×10^4 viable karyocytes in 1 ml of complete culture. The membranes were removed with tweezers after 72 hours (3 days) of cultivation at 37°C and 100% humidity in the open air.

The method of implantation of TM was the following. In the cornea of the animals with pre-induced BK we formed 2 tunnel (to the deep layers of the stroma) incisions, 1.5 mm from the limbus, 1.2 mm wide with orientation at 3 and 9 o'clock. All manipulations were made in the operating room after anaesthesia having been administered to the animals (intravenous administration of Zoletil) and all asepsis and antisepsis rules having been followed. An intrastromal pocket was formed in the layers of the cornea's stroma by a spatula. Then a collet tweezer was inserted into one of the tunnel cuts. It passed through a layered stroma and was taken out through the opposite tunnel incision, where the branches of the tweezer captured TM. During the reverse movement of the forceps, the TM was implanted in the intrastromal corneal pocket. The TM was gently straightened using the spatula. The edges of the tunnel cuts were hydrated.

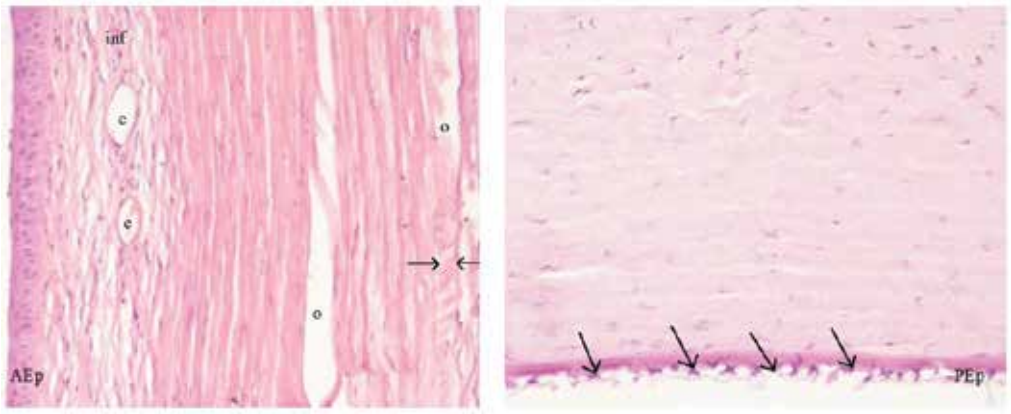
The eyes were enucleated for histological examination 8 weeks after the start of the experiment. The sections of tissues were stained with hematoxylin and eosin, according to Van Gieson's method, and with polychloric dye according to Mallory. LOMO Biolam AU-12 light microscope (Ч7, Ч40, Ч90, microscope's own magnification Ч1.5) and Avtandilov's eyepiece grid of 50 points were used for counting various structural components, specific volumes and cell infiltration. Digital photographs of the histological sections were subjected to morphometric examination using the ImageJ 1.46 software.

The results of the experiment were processed with IBM SPSS Statistics 20. The following statistical parameters were calculated: values of mean M, standard deviation SD, σ and the standard error of the mean m, median Me, 25% quartile Q_1 and 75% quartile Q_3. To assess the initial comparability of the formed groups, Kruskal – Wallis test was used for quantitative data, Fisher's F-test was used for nominal data. Analysis of the dynamics of the indicators was performed using the Wilcoxon paired test, which is used to verify the equality of the average values in two related samples. A parametric Mann – Whitney test (U-test) was used to assess the statistical significance. The differences were considered statistically significant if p was < 0.05.

RESULTS AND DISCUSSIONS

According to the results of light microscopy of the histological sections, the anterior epithelium was represented by a layer of stratified squamous non-squaring epithelium in the animals of the 1st group. The anterior marginal membrane was unchanged. Edema was observed in the cornea stroma (sp. vol. (28.3 ± 10.1)%). There were newly formed vessels (sp. vol. (2.5 ± 1.9)%) and leukocyte infiltration in the anterior third of the stroma (fig. 1, table). Collagen fibers were hydrated and looked swollen with loss of orientation and stained with pikrofuksin. Its tinctorial properties were impaired. The Descemet's membrane was well visualized and was represented by a homogeneous strip. The endothelium was partially absent and was replaced by process-shaped cells.

More pronounced changes of the cornea after TM implantation in the 2nd group of animals were noted. The edema (sp. vol. (18.83 ± 5.8)%), loosening and violation of tinctorial properties of collagen fibers, thin-walled newly formed vessels with a specific volume of (3.2 ± 2.3)% were observed around TM (fig. 2, table). According to histological analysis, the edema of the cornea stroma was more pronounced at the site of TM implantation. The collagen fibers were packed more compactly and retained their normal ability to stain in the anterior segment (between the epithelium and TM). The granulation tissue with full blood vessels was identified near TM. The anterior squamous stratified epithelium was represented by 4-5 layers of cells with normochromic nuclei. The Bowman's membrane was intact. The Descemet's membrane was represented by a homogeneous evenly colored strip. The endothelium was partially absent and was partially replaced by a layer of process cells.



a *b*

Fig. 1. Anterior (*a*) and posterior (*b*) epithelium of the cornea of the 1st group: edema (o), hydrated collagen fibers (horizontal arrows), newly formed vessels (*c*), cellular infiltration (inf), process-shaped cells (slanting arrows). Stained with hematoxylin and eosin, ×200

Рис. 1. Фрагмент роговицы кролика 1-й группы: передний (*a*) и задний (*b*) отделы, отек (о), гидратированные коллагеновые волокна (горизонтальные стрелки), новообразованные сосуды (*c*), клеточная инфильтрация (инф), отростчатые клетки (косые стрелки) на месте заднего эпителия (ЗЭп), ПЭп – передний эпителий. Окраска гематоксилином и эозином, ×200

Таблица
Table

Морфометрические показатели посттравматической реакции роговицы спустя 6 нед от начала моделирования эндотелиально-эпителиальной дистрофии роговицы,
Morphometric indicators of the posttraumatic reaction of the cornea 6 weeks after the start of modelling endothelial epithelial dystrophy, *Me* (Q_1–Q_3)

№ группы Group No	Группа животных Group of nimals	Толщина роговицы, Мкм Corneal thickness, mcm	Отек, уд. объем, % Edema, specific volume, %	Сосуды, уд. объем, % Vessels, pecific volume, %	Фибробласты, клеток в поле зрения, ×200 Fibroblasts, number of cells per vision field, ×200	Лейкоцитарная инфильтрация, число клеток в поле зрения, ×200 Leukocyte infiltration, number of cells per vision field, ×200			
						Лимфоциты Lympho-cytes	Моноциты Mono-cytes	Эозинофилы Eosino-phils	Базофилы Baso-phils
1	ЭЭД роговицы (контроль) Control BK	650 (645–655)	28,3 (26–30)	2,5 (2,3–2,7)	54,3 (51–58)	10,8 (9–11,8)	4,6 (3–5,3)	0,2 (0,1–0,3)	0
2	ЭЭД роговицы + ТМ BK + TM	628* (622–634) $p_1 < 0,05$	18,83* (16–19,3) $p_1 < 0,05$	3,2 (3,1–5,5)	90,1* (86,3–93,7) $p_1 < 0,05$	37,3* (35,6–38,1) $p_1 < 0,05$	8,3 (7–9,9)	11,6* (9,8–12,3) $p_1 < 0,05$	1,1* (0,9–1,3) $p_1 < 0,05$
3	ЭЭД роговицы + ТМ с ПСК BK + TM with PSC	599* (597–603) $p_1 < 0,05$ $p_2 < 0,05$	14,4* (12,9–15,8) $p_1 < 0,05$ $p_2 < 0,05$	6,52 (6–6,8)	132,8* (129,8–134) $p_1 < 0,05$ $p_2 < 0,05$	28,3* (26,8–29,9) $p_1 < 0,05$	3,6 (3,5–3,8)	34,3* (30,1–36,4) $p_1 < 0,05$ $p_2 < 0,05$	3,0* (2,6–3,4) $p_1 < 0,05$ $p_2 < 0,05$
4	ЭЭД роговицы + модифицированная плазмой ТМ с ПСК BK + plasma modified TM with PSC	605* (603–607) $p_1 < 0,05$ $p_2 < 0,05$	12,58* (10,8–13,5) $p_1 < 0,05$ $p_2 < 0,05$	5,35 (5,1–5,5)	159,9* (155,9–163,1) $p_1 < 0,05$ $p_2 < 0,05$ $p_3 < 0,05$	23,3* (20,8–27,1) $p_1 < 0,05$	6,0 (5,7–6,3)	49,3* (46–53) $p_1 < 0,05$ $p_2 < 0,05$	6,1* (5,7–6,5) $p_1 < 0,05$ $p_2 < 0,05$ $p_3 < 0,05$

Примечание. ЭЭД – модель эндотелиально-эпителиальной дистрофии роговицы; ТМ – трековая мембрана; ПСК – пренатальные стромальные клетки.
* p_{1-3} – статистически значимые различия по сравнению с соответствующими группами исследования (*U*-критерий Манна – Уитни).
Note. BK – the model of bullous keratopathy; TM – track etched-membrane.
* p_{1-3} – statistically significant differences compared to the groups 1–3 according to the *U*-test.

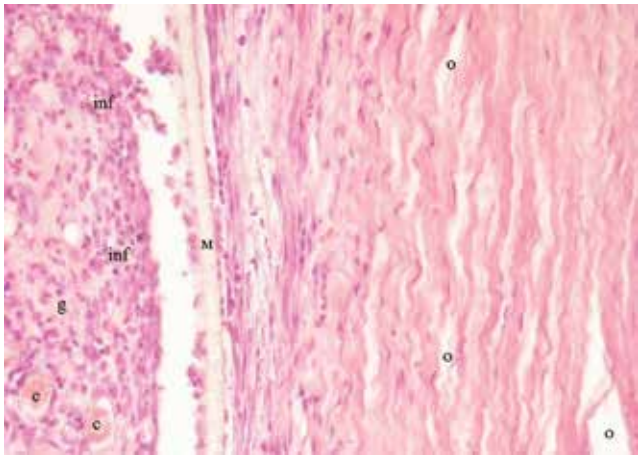


Fig. 2. The corneal fragment of the rabbit from the 2nd group: granulation tissue (g), irregularly pronounced edema (o), full-blooded newly-formed vessels (c), cellular infiltration (inf) at the site of implantation of the TM (M). Stained with hematoxylin and eosin, ×200

Рис. 2. Фрагмент роговицы кролика 2-й группы: грануляционная ткань (гр), неравномерно выраженный интерстициальный отек (о), полнокровие новообразованных сосудов (с), клеточная инфильтрация (инф) в месте имплантации трековой мембраны (М). Окраска гематоксилином и эозином, ×200

The anterior squamous stratified epithelium was preserved throughout the 3rd group of animals. The Bowman's membrane was barely visible. A cluster of fibroblasts ((132.8 ± 26.2) cells in sight, ×200), which had an elongated spindle-shaped or process shaped and oval nuclei, was observed directly under the Bowman's membrane in the cornea stroma (fig. 3, table). Individual cells of the fibroblastis were observed on the TM surface. The irregular edema (sp. vol. (14.4 ± 6.3)%), newly formed blood vessels (sp. vol. (6.52 ± 3.9)%) and leukocyte infiltration represented mainly by lymphocytes and eosinophils were developed in the cornea in the remaining fields of view (fig. 3, table). The collagen fibers looked swollen and had unclear orientation. The Descemet's membrane was represented by a homogeneous strip evenly colored throughout. The endothelium was partially absent and was partially replaced by a layer of process-shaped cells.

The anterior squamous stratified epithelium was represented by 4–5 layers of cells with normochromic nuclei in the 4th group. The Bowman's membrane was intact and unclear. The fibroblasts ((159.9 ± 35) cells, Ч200) and leukocytes accumulated under the Bowman's membrane in the 4th group of animals. Single fibroblasts and leukocytes were detected on the TM surface (fig. 4, table). The newly formed vessels (sp. vol. (5.35 ± 1.15)%), corneal edema (sp. vol. (12.58 ± 5.1)%) and leukocyte infiltration, represented mainly by eosinophils and lymphocytes, were encountered in the stroma (fig. 4, table). The collagen fibers lost a clear orientation and their tinctorial properties. The Descemet's membrane was visualized well and was represented by a homogeneous strip evenly colored throughout. The endothelium was partially absent and was partially replaced by a layer of process-shaped cells.

As a result of the research, it was found that the implantation of TM with preliminary

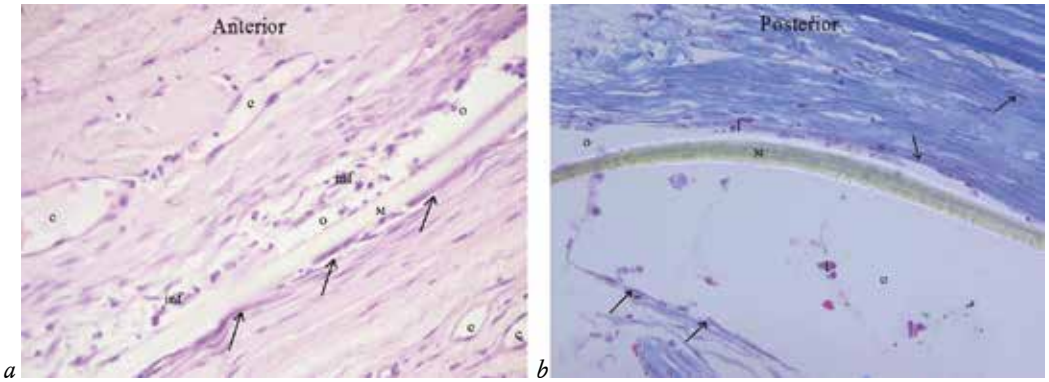
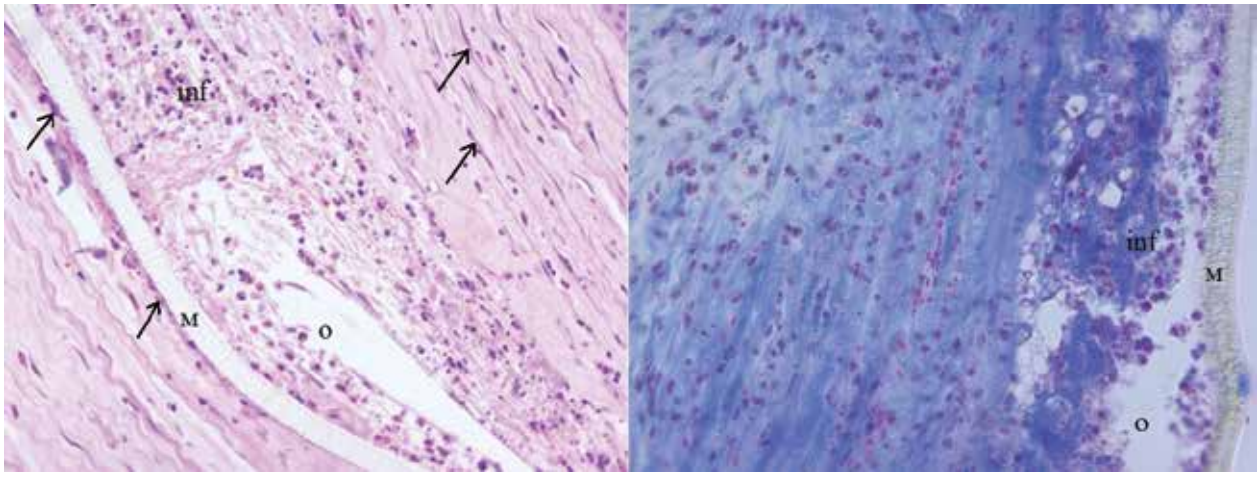


Fig. 3. The corneal fragment of the rabbit from 3rd group: irregular edema (o), new blood vessels (c), single leukocytes (l), cellular infiltration (inf) of corneal stroma and fibroblasts (arrows) on the surface of TM (M) in the 3rd group. Stained with hematoxylin and eosin (*a*) and Mallory polychrome dye (*b*), ×200

Рис. 3. Фрагмент роговицы кролика 3-й группы: выраженный отек (о), новообразованные сосуды (с), единичные лейкоциты (л), клеточная инфильтрация (инф) собственного вещества роговицы и фибробласты (стрелки) на поверхности трековой мембраны (М). Окраска гематоксилином и эозином (*a*), полихромным красителем по Маллори (*b*), ×200



a *b*

Fig. 4. Fibroblasts (arrows) in the cornea stroma, TM (M), leukocyte infiltration (inf), edema (o) in the 4th group. Stained with hematoxylin and eosin (*a*) and Mallory polychrome dye (*b*), ×200

Рис. 4. Фрагмент роговицы кролика 4-й группы: фибробласты (стрелки) в собственном веществе роговицы и на поверхности трековой мембраны (M), инфильтрация (инф), отек (о). Окраска гематоксилином и эозином (*a*) и полихромным красителем по Маллори (*b*), ×200

layering of human PSC promotes the growth of the fibroblast population in the cornea stroma and intensifies leukocyte (lymphocytes and eosinophilic granulocytes) infiltration as opposed to the implantation of PET TM without a cellular component. In addition, the implantation of TM contributes to a twofold decrease in the cornea edema induced by BK. Modification of TM with cold plasma did not affect the studied histomorphometric parameters (table).

CONCLUSION

1) Implantation of TM based on PET in bullous keratopathy contributed to the development of the productive phase of infiltrative inflammation in the cornea of the eye.

2) Pre-layering of human PSC reduced the severity of destructive changes in the rabbit cornea after BK modeling.

3) The modification of TM by cold plasma did not affect the studied histomorphometric parameters.

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Вклад авторов

Филиппова Е.О. – проведение исследований, анализ полученного материала, написание статьи. Кривошеина О.И. – проведение исследований. Пичугин В.Ф. – анализ полученного материала, написание статьи. Хлусов И.А. – проведение исследований (исследования *in vitro*), анализ полученного материала, написание статьи. Дзюман А.Н. – окрашивание препаратов. Зайцев К.В. – проведение исследований *in vitro*.

Authors contribution

Filippova E.O. – carrying out of the research, analysis of the material, drafting of the manuscript. Krivosheina O.I. – carrying out of the research. Pichugin V.F. – analysis of the material, drafting of the manuscript. Khlusov I.A. – carrying out of the research (*in vitro*), analysis of the material, drafting of the manuscript. Dzyuman A.N. – staining. Zaitsev K.V. – carrying out of the research *in vitro*.

Сведения об авторах

Филиппова Екатерина Олеговна, канд. тех. наук, инженер, НИ ТПУ; ассистент, кафедра офтальмологии, кафедра гистологии, цитологии и эмбриологии, СибГМУ, г. Томск. ORCID iD 0000-0003-0425-1213.

Кривошеина Ольга Ивановна, д-р мед. наук, профессор, зав. кафедрой офтальмологии, СибГМУ, г. Томск. ORCID iD 0000-0001-7509-5858.

Хлусов Игорь Альбертович, д-р мед. наук, профессор, кафедра морфологии и общей патологии, СибГМУ; профессор, НИ ТПУ; ст. науч. сотрудник, экспериментальная лаборатория биомедицинских технологий, СибФНКЦ ФМБА России, г. Томск. ORCID iD 0000-0003-3465-8452.

Пичугин Владимир Федорович, д-р физ.-мат. наук, профессор, НИ ТПУ, г. Томск.

Дзюман Анна Николаевна, канд. мед. наук, доцент, кафедра морфологии и общей патологии, СибГМУ, г. Томск. ORCID iD 0000-0002-0795-0987.

Зайцев Константин Васильевич, канд. мед. наук, руководитель экспериментальной лаборатории биомедицинских технологий, СибФНКЦ ФМБА России, г. Томск. ORCID iD 0000-0003-6504-5232.

(✉) **Хлусов Игорь Альбертович**, e-mail: khlusov63@mail.ru.

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Authors information

Filippova Ekaterina O., PhD, Engineer, NR TPU; Assistant, Division of Ophthalmology, Division of Histology, Cytology and Embryology, SSMU, Tomsk, Russian Federation. ORCID iD 0000-0003-0425-1213.

Krivosheina Olga I., DM, Professor, Head of the Division of Ophthalmology, SSMU, Tomsk, Russian Federation. ORCID iD 0000-0001-7509-5858.

Khlusov Igor A., DM, Professor, Division of Morphology and General Pathology, SSMU; Professor, NR TPU; Senior Researcher, Experimental Laboratory of Biomedical Technologies, Federal Siberian Research Clinical Center FMBA of Russia, Tomsk, Russian Federation. ORCID iD 0000-0003-3465-8452.

Pichugin Vladimir F., DPhMSc, Professor, NR TPU, Tomsk, Russian Federation.

Dzyuman Anna N., PhD, Associate Professor, Division of Morphology and General Pathology, SSMU, Tomsk, Russian Federation. ORCID iD 0000-0002-0795-0987.

Zaitsev Konstantin V., PhD, Head of the Experimental Laboratory of Biomedical Technologies, Federal Siberian Research Clinical Center FMBA of Russia, Tomsk, Russian Federation. ORCID iD 0000-0003-6504-5232.

(✉) **Khlusov Igor A.**, e-mail: khlusov63@mail.ru.

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