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COMPOSITE POLYMER MATRICES FOR TISSUE ENGINEERING AND TRANSPLANTOLOGY

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The article presents implementation of modern methods for producing one-, two-, and three-dimensional composite matrices for tissue engineering based on resorbable and non-resorbable polymers. Coagulation method for producing composite fibers based on chitosan and chitin nanofibrils, electrospinning method for composite nanofibers, lyophilization of chitosan solutions and their mixtures with nanoparticles to obtain three-dimensional porous matrices with increased stability of mechanical characteristics in aqueous media have been described. The results of the studies in the adhesion and kinetics of proliferation of stem and somatic cells of humans and animals on the developed matrices were given. *In vivo* experiments showed that materials in the form of fibers, films, tubular samples, and sponges could be used as implants for blood vessels and effective wound dressings. Moreover, the article contains the findings of an investigation into the kinetics of resorption of the involved materials in a living organism.

Keywords: chitosan, chitin nanofibrils, tissue engineering, composite nanofiber, composite sponge

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КОМПОЗИЦИОННЫЕ ПОЛИМЕРНЫЕ МАТРИЦЫ ДЛЯ ТКАНЕВОЙ ИНЖЕНЕРИИ И ТРАНСПЛАНТОЛОГИИ

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В статье представлена реализация современных методов получения одно-, двух- и трехмерных композиционных матриц для тканевой инженерии на основе резорбируемых и нерезорбируемых полимеров. Описаны коагуляционный способ получения композиционных волокон на основе хитозана и нанофибрилл хитина, метод электроформования композиционных нановолокон, метод лиофилизации растворов хитозана и их смесей с наночастицами для получения трехмерных пористых матриц с повышенной стабильностью механических характеристик в водных средах. Приведены результаты исследования адгезии и кинетики пролиферации стволовых и соматических клеток человека и животных на разработанных матрицах. В результате экспериментов *in vivo* установлено, что материалы в виде волокон, пленок, трубчатых образцов и губок можно использовать в качестве имплантатов кровеносных сосудов и эффективных раневых покрытий. Представлены также результаты исследования кинетики резорбции исследуемых материалов в живом организме

Ключевые слова: хитозан, нанофибрилла хитина, тканевая инженерия, композиционное нановолокно, композиционная губка

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Introduction

Tissue engineering is an emerging field based on the principles of materials science, cytology, molecular biology and medicine. The interdisciplinary approach it incorporates is aimed at growing novel engineered tissues for restoring lost function of tissues or organs [1]. Engineered tissue is essentially a biocomposite material consisting of a polymer, ceramic or other matrix, as well as fillers that are stem or somatic cells, growth factors and other components that contribute to proliferative activity of cells, their differentiation, and growth of new tissue. The matrix should be best-suited for reconstructing a new organ or its part: it can be made of fibers, films, three-dimensional porous or tubular scaffolds with different structures and sizes. Recent studies have made it possible to formulate the basic requirements for materials that can be used in tissue engineering and transplantology [2–4].

The strength and deformation properties of the matrix in dry or wet state should allow for sterilization procedures and scaffold engineering. A polymer matrix or engineered scaffold should be convenient to use in surgical implantation into different organs.

In addition, the matrix material should be biocompatible with living tissue, have no negative effect on the surrounding tissues of both the matrices themselves and their resorption products. The matrix surface should facilitate adhesion, proliferation and differentiation of stem and somatic cells as part of an engineered scaffold. To this end, the surface can be modified to obtain the optimal form for the given type of tissue [5].

Materials and equipment

Chitosan (Fluka Chemie, BioChemika line) of molecular weight 255 kDa, degree of deacetylation 80%, and chitin nanofibrils (Mavi Sud s.r.l., Italy) were used to prepare composite fibers.

Chitin nanofibrils were dispersed in water by ultrasonic treatment for 30 min. To obtain a mixture of chitosan solution with chitin nanofibrils, chitosan was added to the aqueous dispersion containing the nanofibrils in an amount necessary to obtain 4 wt.% of solution, and the chitin content was 0.05–20 wt.% with respect to chitosan. A solution of acetic acid was then introduced into the mixture until the acid content in the solvent was 2 wt.%. A mixture of the chitosan solution with chitin nanoparticles was mixed for 90 minutes, filtered, and then air was removed under a pressure of 0.1 atm.

Fibers were prepared in a laboratory setup constructed at the Institute of Macromolecular Compounds RAS. The precipitator was an alcohol-alkaline mixture consisting of a 10% solution of NaOH and methanol in a ratio of 1 : 1. Monofilaments were spun through a die 0.6 mm in diameter; the flow rate of the solution through the die was 0.1 mm/s, the precipitation time was 150 s; the draw ratio λ varied from 40 to 100%. The fiber was washed in distilled water, then dried at a temperature of 50°C.

Nanofibers were produced using a NANON-01A electrospinning system (MECC Co., Japan). The solution was injected through a spinneret using a pump with a radius of 0.3 mm into an electric field with a voltage $V = 18$ kV. The distance between the spinneret and the receiving electrode where the fibers were precipitated was 0.2 m. A cylindrical electrode 1 mm in diameter rotating at a speed of 600 rpm was used to prepare tubular samples.

Chitosan by ALDRICH Chemistry (Iceland), with molecular weight 140 kDa and degree of deacetylation 82%, was used to prepare porous composites. The mixture of the chitosan solution with chitin nanofibrils was prepared similarly to the coagulation method used to obtain fibers by electrospinning. Prepared solutions were kept in a refrigerator for 1 day at $t = 4$°C, and then frozen to $t = -32$°C and kept at this temperature for 4 hours. Samples were lyophilized at $t = -$°5C and a pressure of 1.6 Pa. Lyophilization and freezing of the solutions were done by dry-freezing. The samples were treated with a 10% NaOH solution to convert chitosan from a water-soluble salt to a water-insoluble base.

The prepared samples were coated with a thin layer of platinum; then their structure was studied using a SUPRA-55VP scanning electron microscope (Carl Zeiss, Germany).

Results and discussion

Composite fibers based on chitosan. One-dimensional polymer matrices that can be used as prototypes for nervous and muscle tissues, as well as ligament tissue show great promise for tissue engineering and transplantology. Such matrices are best suited for the fiber structure.

An important problem connected to developing resorbable one-dimensional matrices is obtaining composite fibers characterized by bioresorption of both the polymer and the filler. Introducing chitin nanofibrils into the chitosan matrix allows to produce fully resorbable composite fibers with increased strength and elasticity. The fibers in our study were obtained by wet spinning.

The data from electron microscopy indicate that chitosan fibers obtained by coagulation (wet) spinning have a smooth surface (Fig. 1,*a)* and a homogeneous internal structure. Fibrillar fibers containing chitin nanoparticles typically include flat microfibrils, i.e., layered structures clearly visible on the cleaved surface of the composite fiber in liquid nitrogen (Fig. 1,*b*).

Orientation stretching of composite fibers with small (up to 1 wt.%) filler contents can be described by the following scheme.

As a chitosan molecule interacts with acetic acid (solvent), the amino group undergoes protonation $-NH_2$: $-NH_2 \rightarrow NH_3^+$; chitosan acetate, a salt, forms as a result.

There is a free volume between chitin nanoparticles where the macromolecules of chitosan acetate and acetic acid are located.

The solution passing through the spinneret enters the shear stress field, and both the filler particles and the chitosan acetate macromolecules become oriented as a result. Due to good adhesion, chitosan acetate macromolecules located in the surface layer of chitin nanofibrils acquire an additional orientation. Chitosan acetate macromolecules become oriented upon stretching in the coagulation bath, an oriented crystal structure forming. Further increase in stretching during formation of composite fibers contributes to the orientation of macromolecules in intercrystalline amorphous regions inside chitosan fibrils.

After the solution passes through the spinneret and the jet contacts the precipitant (alcohol-alkaline mixture), the macromolecules undergo deprotonation and the polymer transformed from salt to base form. Shear stresses in the die and stretching of the fiber after precipitation contribute to oriented structure of both polymer macromolecules and filler nanoparticles [6].

Chitosan fibers are not cytotoxic, which is confirmed by effective adhesion of mesenchymal stem cells on their surface. Fig. 2 shows micrographs of the fiber surface with visible aggregations of mesenchymal stem cells. Cells have a typical morphology and growth structure. Not only cell adhesion but also proliferation on the fiber surface can be observed in the micrographs, recording the time of mitosis. The surface of the fiber obtained with a high draw ratio ($\lambda = 100\%$) has a fibrillar structure, containing inhomogeneities in the form of channels along the fiber. Cells have an elongated shape on such a surface.

The effect of the surface morphology of the matrix on the shape of fibroblasts was considered in [7, 8], where it was established that the changes in the shape of stem cells is one of the factors of their directed differentiation.

Porous films based on composite nanofibers

Metabolic processes promoting effective proliferation in the cell require optimal transport characteristics of the matrix, in particular, high gas and water permeability [9]. Film materials based on nanofibers from biocompatible polymers have such properties.

Aliphatic copolyamide (CoPA) is highly

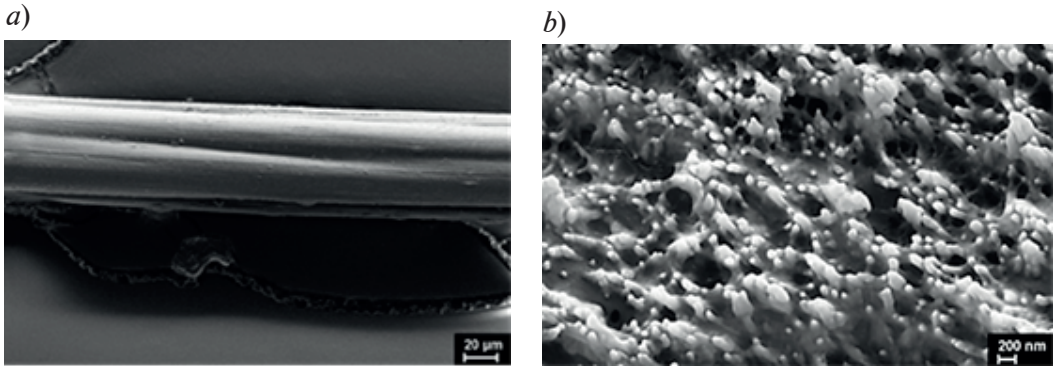

Fig. 1. Micrographs of composite fiber based on chitosan containing 1 wt.% chitin nanofibrils: fiber surface (*a*), cross-section (*b*)

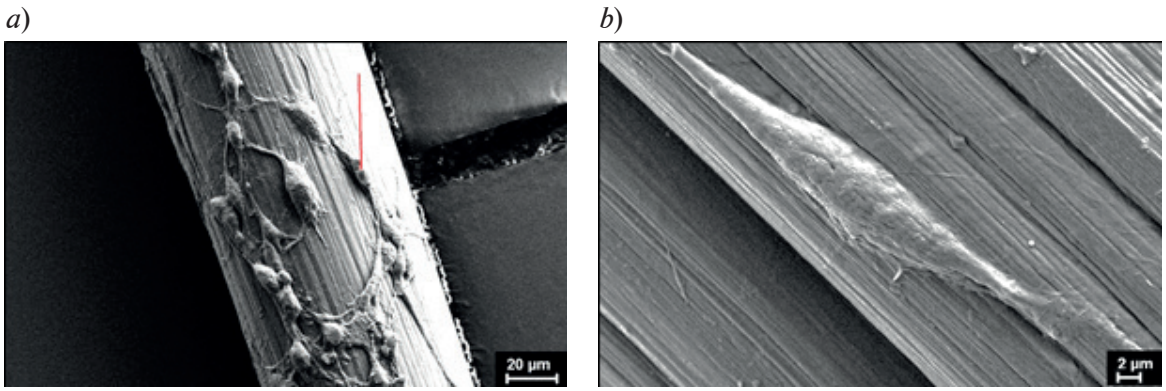

Fig. 2. Micrographs of surface (with varying magnifications) of chitosan fibers after cultivation of mesenchymal stem cells for 3 days
The arrow indicates the region of mitotic cell division

dielectric, its solutions are capable of phase separation, and this solvent is environmentally friendly, making it a good candidate for preparing nanofibers by electrospinning [9].

To make the nanofibers, we used CoPA, a copolymer of ε-caprolactam

$$[-NH-(CH_2)_5-CO-]$$

and hexamethylenediaminadipinate

$$[-NH-(CH_2)_6-NH-CO-(CH_2)_4-CO-]$$

in a 40:60 ratio.

We have found previously that CoPA solutions with a concentration of 16 wt.% dissolved in an 80/20 ethanol/water mixture have the optimal properties for electrospinning of fibers.

We have established that porous films based on CoPA nanofibers are characterized by relatively low strengths (σ = 6.5 MPa) and elastic moduli (E = 55 MPa). However, films with such mechanical characteristics can be successfully manipulated in air and in liquid media. The films are elastic both in dry and in wet conditions, duplicating the surface morphology fairly well. Materials with such properties are quite suitable as matrices for tissue engineering, as well as as part of composite wound dressings.

The CoPA macromolecule contains amide, carbonyl and carboxyl groups, including mainly covalent and hydrogen chemical bonds. A material based on such a polymer is hydrophilic. CoPA fibers and films preserve their size and properties during prolonged contact with aqueous media. It then seems reasonable to assume that the materials obtained should have good adhesion to stem and somatic cells, ensuring a high rate of cell proliferation both on the surface and in the bulk.

Chitosan is another polymer successfully used for different medical applications. It was established in [15] that introducing up to 20 wt.% chitin nanofibrils into a chitosan solution increases the mixture's viscosity on the one hand, strengthening its dependence on the shear rate on the other hand. This is due to the

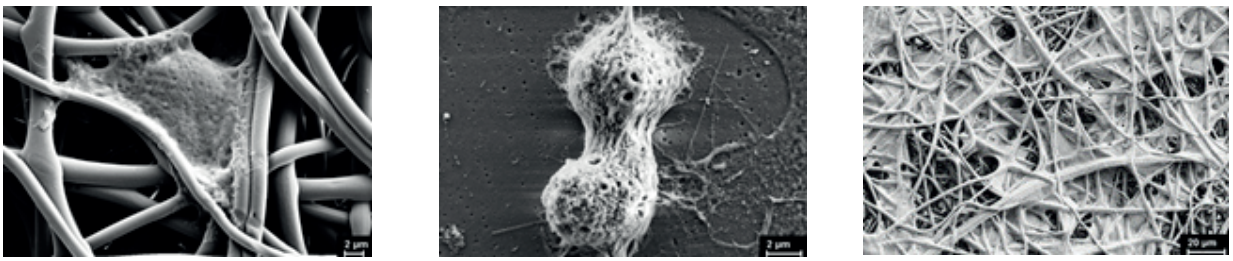

Fig. 3. Electron micrographs of tissue-engineered scaffolds, including two types of matrices: based on nanofibers made of CoPA and mesenchymal stem cells (*a*, *b*) and based on nanofibers made of chitosan and human fibroblasts (*c*);
stem cell adhesion on a matrix (*a*), division of this cell (*b*)

forming cluster structure of filler particles and the orientation of chitin nanofibrils induced by the shear stresses in the electromagnetic field. Chitin nanofibrils facilitate the formation of nanofibers in the electric field, leading to a significant reduction in the number of defects.

Fig. 3 shows electron micrographs of an engineered tissue scaffold including a matrix based on nanofibers made from CoPA and mesenchymal stem cells (Fig. 3,a,b), chitosan and human fibroblasts (Fig. 3,c).

The micgrographs show the cell's pseudopodia contacting the matrix nanofibers (Fig. 3,*a*), stem cell division (Fig. 3,*b*) and the scaffold's structure (Fig. 3,*c*).

Blood vessel grafts based on polylactide nanofibers

Electrospinning is one of the most promising methods for engineering blood vessel grafts, allowing to obtain materials based on nanofibers with high porosity and large specific surface area. The latter is especially important for cell migration and proliferation inside the graft. The structure should prevent blood from oozing through the walls of the tube [10–13]. Electrospinning produces nanofibers with a sufficient level of mechanical characteristics of tubular grafts that should be integrated into a living body. The inner surface of the grafts should be lined with an endothelial layer at an early stage of implantation, significantly reducing the risk of blood clots.

We prepared a tube with an inner diameter of 1 mm and a wall thickness of about 250 μm (Fig. 4,*a*) by electrospinning. The nanonfibers were spun from a solution of polylactide in dichloroethane onto a rotating receiving electrode [13].

In vivo studies consisted of grafting tubular scaffolds based on PLA nanofibers into the abdominal aorta of rats. We establish that all grafts were permeable after 4 weeks; the aorta was attached to the graft; removal of sutures did not lead to disruption of the anastomosis; no pathological effect on the surrounding tissue was found.

Morphological analysis of the material [3] revealed an endothelial layer starting with distal and proximal anastomoses formed on

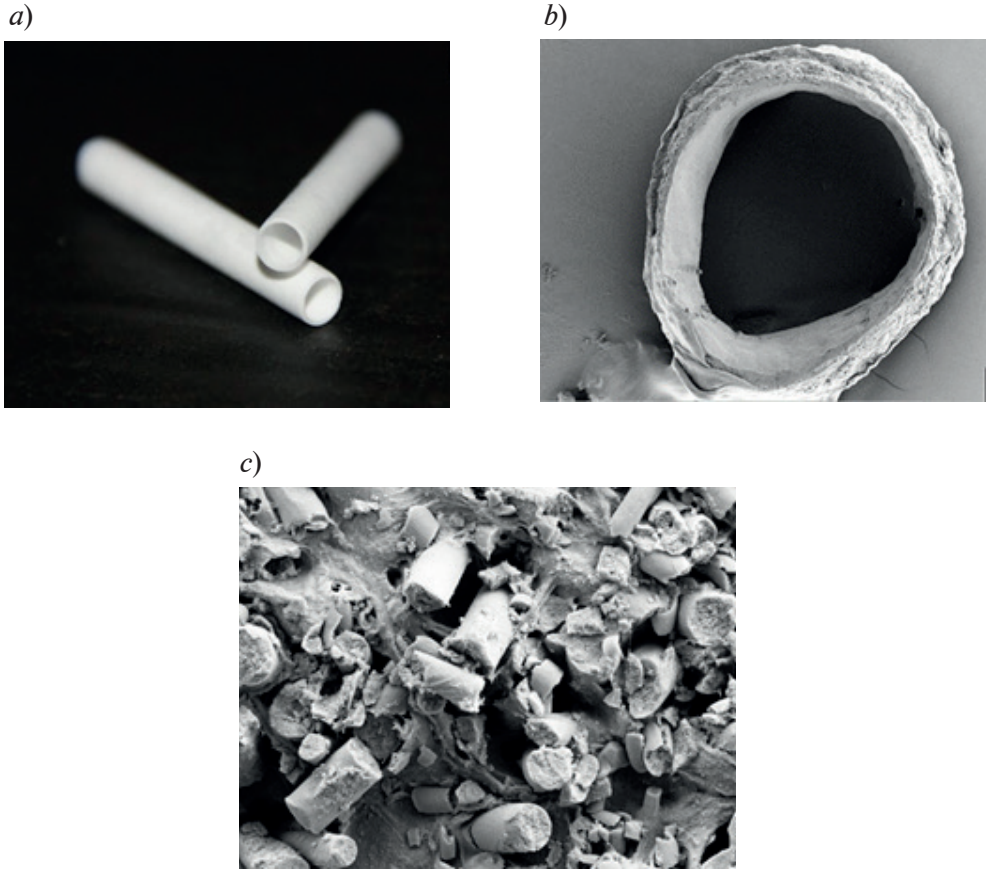

Fig. 4. Photograph of vascular grafts based on PLA nanofibres (*a*) and micrographs of their cross-section with different magnifications (*b*, *c*) 64 weeks after implantation

the inner side of the graft; the central part was lined with an inhomogeneous reticular fibrin layer. Fibroblast nuclei were found between the PLA layers, mainly near the adventitia; thin collagen fibers began to appear. Foreign-body giant cells were located on the outer side of the graft. These cells are generated in response to a foreign body and actively participate in eliminating it. However, the cells were not large enough to penetrate through the pores into the graft in our case; they retained their shape and structure.

The first signs of bioresorption were detected 12 weeks after implantation. All grafts remained permeable 24 weeks after implantation but multiple cross cracks appeared on the nanofibers and a significant portion of the fibers were fragmented. This points to intense resorption of the polymer matrix.

It can be seen from the cross-section shown in the micrograph taken 64 weeks after implantation (Fig. 4, *b*, *c*) that the porosity of the graft walls decreased substantially. Morphological studies indicate that endothelium and subendothelium containing collagen fibers completely cover the graft, and a neointima formed. Fibroblasts and newly formed collagen fibers are located within the graft between PLA fibers. Numerous foreign body giant cells were found near the adventitia.

Wound dressings based on composite nanofibers

The wound dressing should ensure gas and moisture exchange necessary for maintaining vital functions of cells, reproduce the surface morphology of the wound and be convenient for surgical manipulations. Modern wound dressings are atraumatic and can be removed from the wound without damaging or destroying the epithelial layer. Finally, the dressing material should protect the wound from contamination with pathogenic microflora from the environment.

Porous films based on polymer nanofibers produced by electrospinning have all of these properties [10]. Nanofibers produced from alcohol-soluble aliphatic copolyamide (CoPA) were described in [9]; composite nanofibers based on chitosan and chitin nanofibrils in [15].

We earlier developed a method for producing composite wound dressings based on CoPA nanofibers and composite nanofibers of chitosan and chitin nanofibrils based on the specific properties of each material [16].

Non-resorbable CoPA nanofibers give the material the necessary mechanical characteristics, maintaining exchange processes between the wound and the environment and protecting against pathogenic bacteria and fungi (Fig. 5,*a*).

The layer that directly contacts the wound, consisting of composite nanofibers based on chitosan and chitin nanofibrils (Fig. 5,*b*), provides an atraumatic coating, contributing to effective regeneration of integumentary tissue.

The material fabricated is biocompatible and has a porous structure preserving the shape and size of pores in liquid biological media. The mechanical characteristics of the material allow to modify it both in dry and in wet conditions. As the dressing is applied to the wound, the layer consisting of composite nanofibers based on bioresorbable natural polymers (chitosan and chitin) and directly

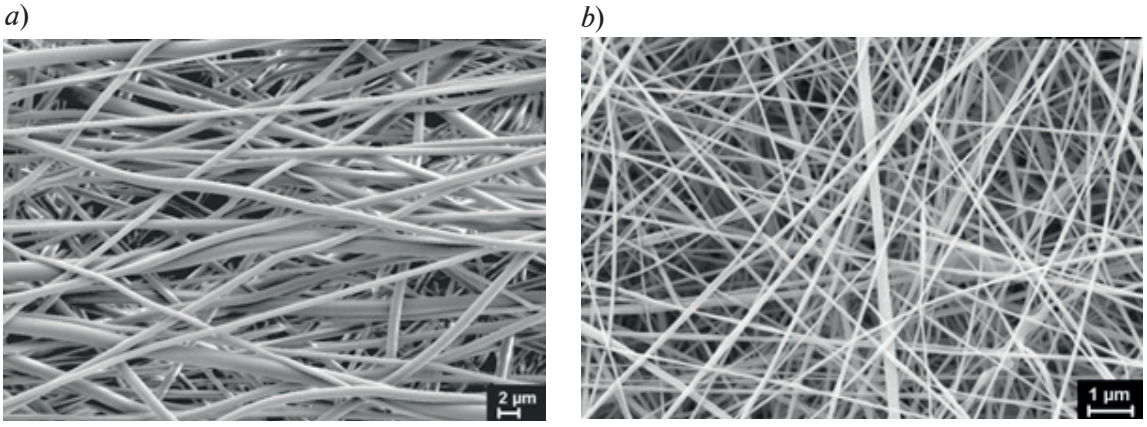

Fig. 5. Micrographs of nanofibers made of CoPA (*a*) and composite nanofibers based on chitosan and chitin nanofibrils (*b*)

contacting the damaged surface resorbs under the action of an active biological medium. The active medium includes white blood cells, mast cells, plasmocytes, histiocytes, fibroblasts, glycosidases and chitinases. Chitin, chitosan and their biodegradation products have a bactericidal effect on the medium, favoring granulation and epithelization of the wound. The dressing is bilayered, so only a durable non-resorbable layer is separated when the dressing is replaced or removed, and granulation and epithelialization processes in the wound are not disrupted. A less durable layer consisting of chitin and chitosan, which is partially resorbed, remains on the wound surface until complete resorption and facilitates healing.

We studied the obtained material in vivo as a wound dressing for treating third-degree skin burns (according to the tenth revision of the International Classification of Diseases, ICD-10). The experiment was conducted on male Wistar-Kyoto rats each weighing 200–250 g. The composite dressing was applied to the wound in the experimental group. The animals were observed for 4 weeks.

Table 1 shows wound surface areas for a third-degree burn in the groups treated with the dressing we developed, the G-DERM dressing and in the control group.

It follows from the data given in Table 1 that the healing rate of a burn wound is considerably faster for treatment with a composite dressing based on CoPA nanofibers and composite nanofibers made of chitosan and chitin nanofibrils, compared to a similar material that is widely available in the market, and also much faster compared to the control group.

Three-dimensional porous composite matrices

Most human and animal organs are three-dimensional structures of different shapes. Each of these organs has its own important morphological and physiological features, which should be taken into account in developing matrices for engineered tissue scaffolds. Open porosity is a crucial parameter of three-dimensional matrices for cell technology. Pore size should be sufficient to ensure uniform filling of the free volume of the matrix with somatic cells, their migration and proliferation. Pore structure should facilitate the metabolic processes necessary for the vital functions of cells.

Some polymers are capable of forming different types of porous structures [1–3]. Chitosan is one of these polymers. It can be seen from Fig. 6,*a* that phase separation occurs in a frozen mixture of chitosan solution with chitin nanofibrils. The polymer containing the filler forms a reticular structure. Composite sponges obtained by lyophilization

Table 1

Treatment efficiency for two wound dressings compared by wound surface area for third-degree burn

Observation time, days	Wound surface area, cm^2		
	Synthesized wound dressing	G-DERM dressing	No dressing (control group)
0	32	32	32
3	22	27	29
7	16	19	25
15	9	12	18
21	1.5	8.0	12.5

Note. The experiment was conducted on male Wistar-Kyoto rats each weighing 200–250 g.

characteristically have a pronounced laminar structure (Fig. 6,*b*), compared with that of sponges made of pure chitosan.The data given in literature indicate that the resorption rate of the chitosan matrix depends on the degree of deacetylation, the molecular weight of the polymer, the porosity of the materials, the presence of nanoparticles or other polymers in the matrix [13, 14].

Fig. 7 shows micrographs of a cross-section of a chitosan-based material. Apparently, the material has an open-pore structure; pores are connected with each other and with the environment. This structure allows nutrients and dissolved gases to circulate freely within the entire matrix. Pore size and tortuosity of the channels connecting the pores to each other enable free cell migration.

Table 2 shows the results of a histological study of porous chitosan matrices. Moderate aseptic inflammation around the matrix was detected 1 week after graft implantation, with leukocyte infiltration centers and predominant segmented nuclei. Mild aseptic inflammation was observed around the porous matrix 2 weeks after implantation, however, neither connective tissue capsules or edema were found. No connective tissue capsules were found around the porous matrix 6 weeks after implantation. The cross-sectional area of the matrix decreased to $5.38 \cdot 10^5 (\mu m)^2$ 3 months (12 weeks) after implantation; this value is noticeably different from that measured a week after implantation (65.9%).

The cross-sectional area of the matrix decreased to $2.64 \cdot 10^5 (\mu m)^2$ 6 months (24 weeks) after implantation, which is drastically different from the values obtained 1 and 6 weeks after implantation. Fragments of the chitosan matrix could be detected in a single tissue sample 12 weeks after implantation. The cross-sectional area of the matrix decreased to $1.71 \cdot 10^5$ $(\mu m)^2$.

It was thus established that complete bioresorption of the chitosan matrix occurs 12 months after implantation; scar tissue did not form, and no change or damage was found in the surrounding tissues. The shape of the

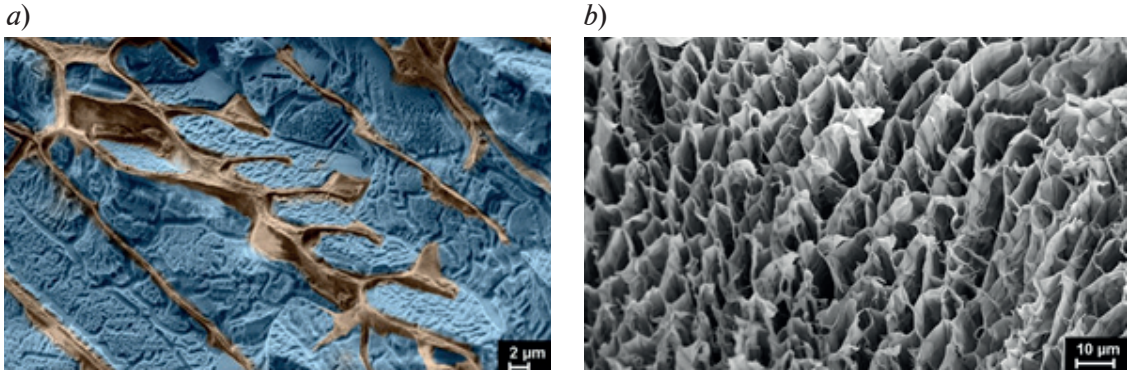

Fig. 6. Micrographs of chitosan solution mixture with chitin nanofibrils at −160°C (*a*) and sponge after lyophilic drying at −5°C (*b*)

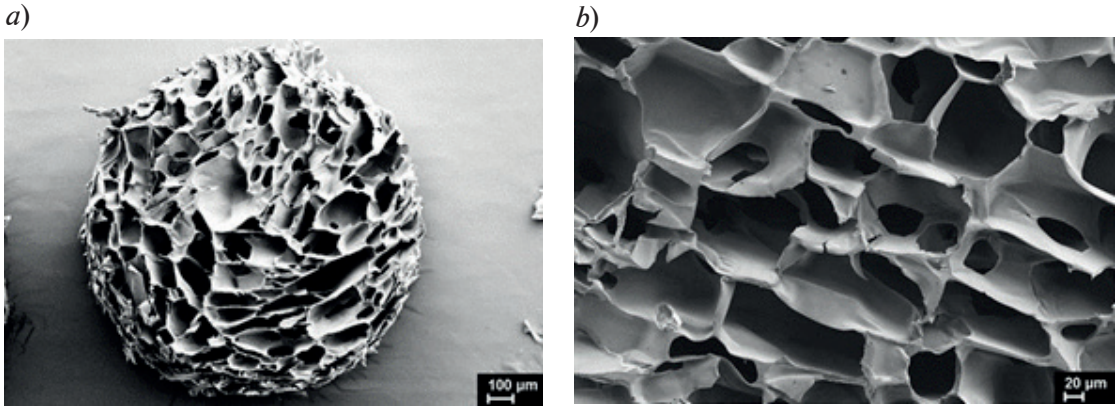

Fig. 7. Micrographs of cross-section of cylindrical sponge scaffold: general view (*a*), same sponge with large magnification (*b*)

Table 2

Volumetric content of components in porous composite matrix based on chitosan after implantation in rat muscle

Observation time, weeks	Volumetric content of component, %			
	Matrix	Collagen fibers	Vessels	White blood cells
1	17.74	0.94	0.12	11.94
2	19.10	3.24	0.48	0.86
6	19.38	3.94	0.88	1.20
12	24.70	3.40	0.50	1.63
24	24.90	3.74	1.30	3.90

Note. The experiment was conducted on a male Wistar-Kyoto rat weighing 250 g. The graft was inserted in the latissimus dorsi muscle.

matrix was highly stable throughout the experiment, with the matrix preserving an open pore structure, facilitating blood vessel invasion and free migration of cells in the matrix.

Conclusion

Composite fibers and nanofibers based on chitosan and chitin nanofibrils have been obtained by coagulation and electrospinning. We have proposed a mechanism for synthesizing composite fibers containing anisometric nanoparticles. In vivo studies of tubes based on polylactide nanofibers as blood vessel grafts were conducted on rats. We have developed composite wound dressings based on nanofibers made of aliphatic copolyamide and composite nanofibers made of chitosan and chitin nanofibrils. The in vivo study confirmed the high efficiency of the developed wound dressing for treating deep skin lesions of different etiologies. Considering the resorption kinetics of three-dimensional porous sponges based on chitosan and tissue (connective, nervous, epithelium) formation, we can recommend this material for tissue engineering, in particular for bone tissue reconstruction.

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