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Morphological changes in fibrous tissue of rat myocardium after administration of dispersed allogeneic biomaterial

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Abstract

To improve the structure of the heart muscle after myocardial infarction, methods of regenerative medicine are used. One of the promising areas is the intra-myocardial administration of acellular allogeneic biomaterial (AB). The AB stimulates the regeneration of organs and tissues. But, the effect of AB on the myocardium after its fibrous ischemic degeneration has not been assessed. The aim of the study was to assess the morphological structure of the heart after cryodestruction in the late period and the use of AB. Chronic myocardial infarction was modeled in 80 male rats. To simulate chronic myocardial infarction and fibrosis formation, contact cryodestruction was performed. After 45 days, during repeated thoracotomy in the main group, AB suspension was injected into the area of the cryogenic myocardial scar. Six injections of 0.50 mg of dry substance were administered. In the control group, physiological solution was injected. After AB administration, following 7, 14, 30, and 45 days, the animals were withdrawn from the experiment, and the hearts were excised for histological and immunohistochemical studies. The AB underwent gradual phagocytosis by macrophages and gradually replaced by loose fibrous connective tissue with the presence of cardiac troponin I^+ labeled muscle cells, which over time underwent hypertrophy. Cardiomyocytes were grouped in the AB implantation zone as separate clusters. The heart mass did not change in both experimental groups. The use of AB in the area of the formed cryogenic myocardial scar promoted the transformation of dense fibrous connective tissue into loose tissue and its replacement with cardiac muscle tissue.

Introduction

Stimulating regenerative processes in damaged tissues is one of the current trends in modern medicine.[1-7] Success in this area is accurately associated with the improvement of cell therapy.[8,9] To obtain tissue-specific regenerations, it is proposed to use tissues with a high content of appropriate resident stem cells or progenitor cells.[10,11] At the same time, the problem of overcoming the transplantation stress to which the implanted cellular material is exposed remains relevant.[12] However, an equally promising approach for targeted influence on the regeneration process is the use of acellular biomaterials capable of stimulating the endogenous reparative capabilities of tissues. The sources of such acellular biomaterials are derivatives of the extra-cellular matrix (ECM).[13-15] Similar materials include allogeneic biomaterial (AB), made from decellularized ECM. It stimulates the regeneration of organs and tissues.[16] In the authors' previously published works, it was shown that, in the experiment, the use of AB helps prevent cardiosclerosis in the acute and subacute stages of myocardial infarction.[17,18] The AB biodegradation products initiated both the chemoattraction of pluripotent stem cells and their differentiation and integration.[19] At the same time, the importance of using ECM to stimulate cardiomyogenesis was demonstrated. However, there are obvious limitations to its use in the area of fibrous tissue. It is believed that it is currently impossible to initiate the reverse development of the scar.[20] However, achieving such an effect would have obvious practical implications. At present, the possible participation of ECM-based biomaterials in the involution and/or remodeling of cardiosclerosis is practically not covered. *In vivo*, the ECM is a complex network consisting of many components, including collagens, adhesion molecules, proteoglycans, and glycosaminoglycans. The

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unique structure of the ECM is known to play a vital role in determining cellular adhesion, proliferation, differentiation, and polarity, and tissue-specific cells migration.[21,22]

The goal of the study was to evaluate the morphological structure of the heart after the use of AB against the background of cryogenic cardiosclerosis.

Materials and Methods

The study included 80 laboratory animals (Wistar male rats weighing 0.20-0.25 kg). The animals were divided into two groups, including control (n = 40) and main (n = 40). All animals were exposed to the damaging effects on the heart muscle using the cryodestruction method. This method allows for obtaining lesions of the same volume and localization.[23] Before exposure, the animal was anesthetized by intra-muscular injection of a zoletil solution (Virbac, Carros, France) at a dose of 1.00 mg kg^{-1} and fixed in a supine position. The animal's chest was opened, and a section of the left ventricle in the area of the apex of the heart was frozen with a massive metal stylet previously placed in liquid nitrogen. The working surface was the flat end of the stylet 6.00 mm in diameter, which was applied without pressure to the heart surface for 10 sec. Then, the wound was sutured in layers. Previous studies have shown that the remodeling effect of cryoinjury performed according to this protocol on the heart muscle is comparable to the effect of coronary artery stenosis.[24,25] Forty-five days after cryodestruction, during repeated thoracotomies in the main group, an AB suspension was injected into the area of cryogenic myocardial necrosis. Each injection contained 0.50 mg of dry substance and did not exceed 10.00 μL in volume. Before use, AB was diluted with 0.90% saline. Each animal received six intra-myocardial injections of the AB suspension. The total amount of administered biomaterial was 3.00 mg *per* animal, in accordance with previous researches.[18-20] Animals in the control group received a 0.90% saline solution in the same volume. The AB used was a dispersed form of acellular ECM with a particle size of 50.00 - 80.00 μm, developed at the Federal State Budgetary Institution, All-Russian Center for Eye and Plastic Surgery, Ministry of Health of the Russian Federation, Ufa, Russia. The biomaterial was manufactured according to the Technical Standard No. 42-2-537-87 and certified and approved for use in clinical practice by order of the Union of Soviet Socialist Republics Ministry of Health No. 87 901-87 dated July 22, 1987. For this study, the AB was made from rat tendons.

The animals were kept in vivarium conditions with free access to water and food. All manipulations were carried out in accordance with the provisions of the Order of the Ministry of Health of the Russian Federation dated 01.04.2016 No. 199n. Rats were withdrawn from the experiment 3, 7, 14, and 45 days after the injection of AB or saline. For euthanasia 0.15 mg kg^{-1} xylazine (Interchemie, Venray, The Netherlands) was used according to the Council Directive 86/609/EEC. There were 10 animals for each research point. The hearts of animals removed from the experiment were fixed in a 10.00% solution of neutral formaldehyde, dehydrated in a series of alcohols of increasing concentration, and embedded in paraffin according to the generally accepted method. Sections were prepared using a Leica RM 2145 microtome (Leica Microsystems Nussloch GmbH, Nußloch, Germany) and stained with Hematoxylin and Eosin, van Gieson, and Mallory. For immunohistochemical studies, 4.00-μm paraffin sections were stained using a Leica Microsystems Bond™ immunohistostainer. The cluster of differentiation 68, diluted 1 / 300 (Santa Cruz Biotechnology, Dallas, USA), and cardiac troponin I type 3, diluted 1 / 150 (Cloud-Clone Corp., Wuhan, China), were used as the primary antibodies. For unmasking, an indirect streptavidin-biotin detection system, Leica BOND (Novocastra™), was used. The reaction specificity was assessed by staining sections without the primary antibodies.

The two-factor analysis of variance method was used. Data analysis was performed using non-parametric (rank) methods, including one-factor analysis of variance according to Kruskal-Wallis and comparison of uncorrelated data by the Mann-Whitney method. Medians and variation limits were used.[26] The diagram was constructed in the Statistica 6.0 program (Dell Inc., Round Rock, USA). The study and visualization of the preparations were performed using a Leica DMD 108 light microscope with specialized software for managing settings and capturing images.

Results

Forty-five days after cryodestruction, an avascular scar was observed in the myocardium. It was represented by dense fibrous connective tissue. It consisted of thickened, unidirectional bundles of collagen fibers with fibroblastic infiltration. Three days after AB implantation, signs of proliferation of loose fibrous connective tissue were detected, along with a developed network of hemo-capillaries. They had different directions and thin walls, formed anastomoses, varied in size, and contained blood cells. There were no signs of stasis or sludge. The collagen fibers had a loose architecture with an amorphous substance between them. Macrophages were determined in large quantities near the AB particles (Fig. 1A). Signs of cardiomyocyte hypertrophy were observed after 7 days. Cardiac muscle cells were elongated in one direction. Also, binuclear cardiomyocytes were determined. After destruction, myocytes from the remaining healthy areas of the myocardium grew into widened inter-fiber spaces (Fig. 1B). These cells showed cardiac troponin I and regular

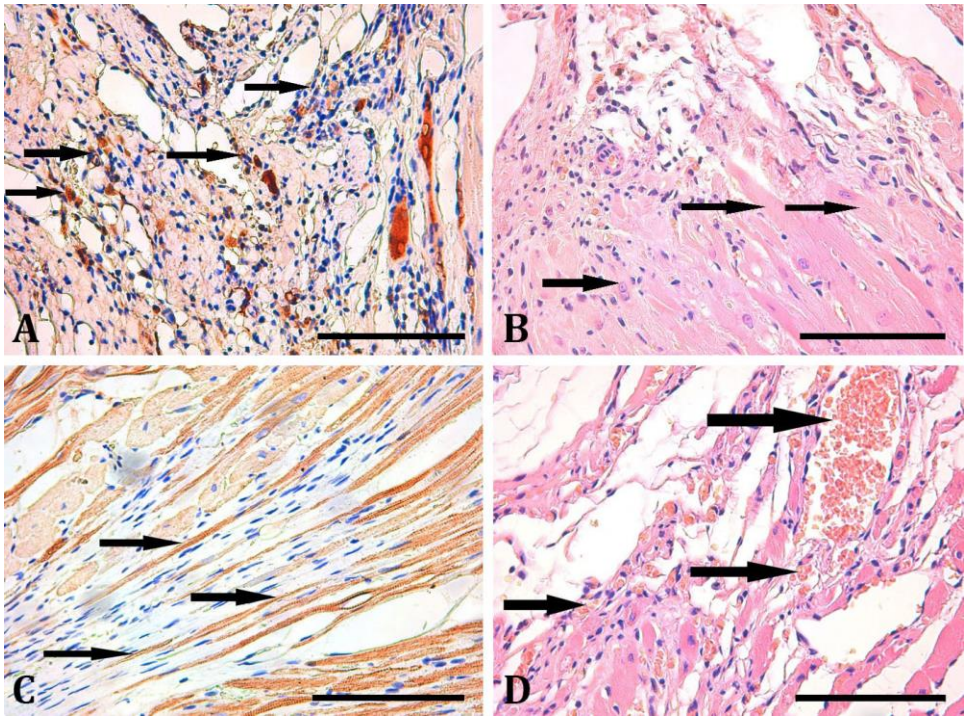

Fig. 1. The state of fibrotic myocardium after the use of acellular allogeneic biomaterial in the early stages. **A)** Intensive vascularization and infiltration of cluster of differentiation 68^{+} cells (arrows) in the scar after 3 days (indirect immunoperoxidase method for detecting cluster of differentiation68 with Hematoxylin counterstaining, bar = 100 μm); **B)** Cardiomyocyte hypertrophy (arrows) after 7 days (Hematoxylin and Eosin staining, bar = 100 μm); **C)** Cardiac troponin I (arrows) after 7 days (indirect immunoperoxidase method for detecting cardiac troponin I with Hematoxylin counterstaining, bar = 100 μm); **D)** Muscular-connective tissue regenerations were vascularized after 14 days. Newly formed blood vessels are evident (arrows; Hematoxylin and Eosin staining, bar = 100 μm).

cross-striations (Fig. 1C). After 14 days, the muscle-connective tissue type of the regeneration was detected. In the inter-fiber spaces of the collagen bundles, scattered cardiac muscle cells were observed that did not form cellular contacts with each other through intercalated discs. They were small in size, mononuclear, and mainly localized near the blood vessels. By this time, the blood vessels were represented by an abundant network of hemocapillaries (Fig. 1D).

After 45 days, foci of cardiac muscle cell clusters were observed in the cryodestruction zone, the nuclei of which were located centrally. The cells were concentrated in the form of clusters, separated from each other by thin connective tissue layers (Fig. 2).

A fundamentally different histological picture was observed in the control group after the injection of saline into the area of the fibrotic myocardium. After 3 days, a scar was visible, represented by dense avascular fibrous connective tissue infiltrated with fibroblastic cells (Fig. 3A). After 14 days, the morphological structure of the tissue did not change in the control group. Collagen fibers of dense fibrous connective tissue sealed the remaining cardiomyocytes adjacent to the scar. After 45 days, against the background of developed fibrosis and prolonged hypoxia, even ossification was detected in the damaged tissue (Fig. 3B).

The data regarding the total lumen area of hemo-capillary vessels obtained in both groups were modifications of the normal distribution (the maximum absolute difference (D_{max}) = 0.11; $p > 0.20$ for both samples) and could be analyzed by parametric methods. In addition, the use of Levene's test showed that these data can be processed by Fisher's parametric analysis of variance (Fisher criterion (F) = 0.40; $p > 0.66$ and F = 2.90; $p > 0.06$ for the main and control groups, respectively). In the main group, the dependence of the average size of the total capillary lumen area (TLA) turned out to be insignificant (F = 2.76; $p > 0.07$).

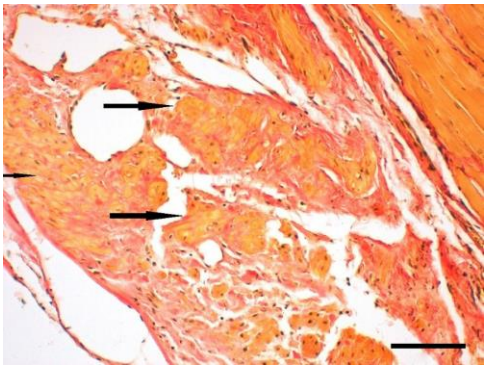

Fig. 2. Clusters of cardiomyogenic cells (arrows) 45 days after the use of allogeneic biomaterial (van Gieson staining, bar = 100 μm).

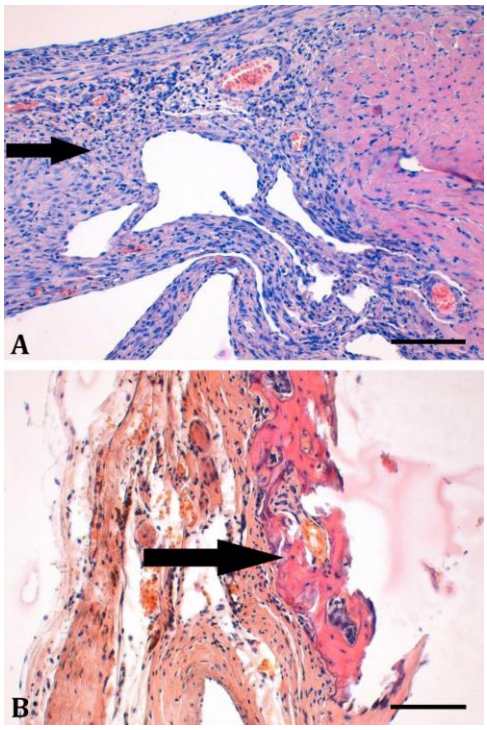

Fig. 3. The state of fibrous myocardium in the control group. **A)** Cardiosclerosis 7 days after the administration of saline solution (arrow); **B)** Ossification (arrow) 45 days after the administration of saline solution (Hematoxylin and Eosin staining, bars = 100 μm).

On the 45th day, the average TLA was significantly higher ($p < 0.02$) than the 7th day (8,028.40 ± 2,770.30 mm^2 *versus* 6,508.00 ± 2,404.30 mm^2). On the 14th day, this indicator was intermediate (7,053.40 ± 2,567.60 mm^2) and did not differ significantly from the levels of the 7th ($p > 0.56$) and 45th days ($p > 0.09$). However, it is clear that the coefficient of variation at all observation periods is about 30.00 - 40.00%. Therefore, the differences were tested by the non-parametric Mann-Whitney criterion. The difference between days seven -14 and days 14 - 45 also turned out to be insignificant ($p > 0.57$ and $p > 0.26$, respectively). However, the difference between the 7th and 45th days was also insignificant ($p > 0.06$). Consequently, the level of TLA in the group of animals received AB injections can be considered stable throughout the observation period.

In the control group, the dependence of the average level of TLA in the observation time was generally significant ($F = 4.50$; $p < 0.02$) and manifested in the fact that the average level of this parameter on the 14th day (508.60 ± 178.30 mm^2) was significantly lower ($p < 0.02$ and $p < 0.009$, respectively) than the 7th (724.40 ± 272.00 mm^2) and 45th days (686.90 ± 188.90 mm^2). The difference between the 7th and 45th days was insignificant ($p > 0.86$). Thus, the results of the parametric analysis were confirmed, and on the 14th day in the control group, there was actually a significant decrease in TLA.

In an inter-group comparison, it turned out that starting from the 7th day, the TLA after the administration of AB became significantly higher than the control group. Moreover, this pattern of changes increased by the 45th day in the main group (Fig. 4).

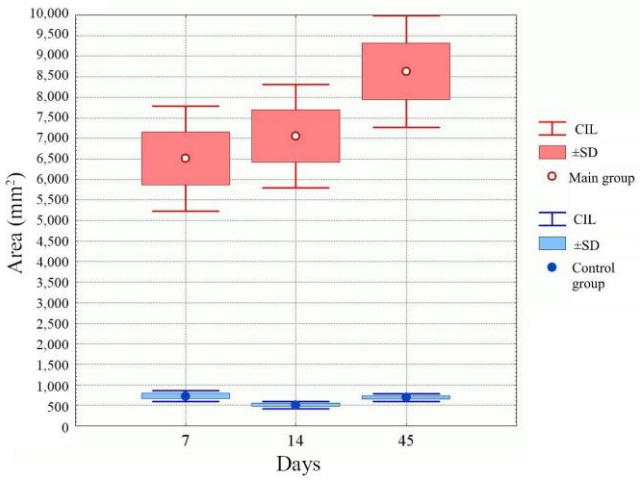

Fig. 4. Average level of total capillary lumen area (mm^2) in the main and control groups at different observation periods (days). The abscissa axis shows periods (days). On the ordinate axis, the thickness is the total diameter (μm). CIL: Confidence interval limits; SD: Standard deviation.

Thus, the intra-myocardial use of AB into a formed myocardial scar developed at the site of cryodestruction initiated the transformation of dense fibrous connective tissue into loose fibrous tissue with a large number of newly formed blood vessels. Implantation of the biomaterial initiated the activation of macrophages. After using AB, signs of myocardial hypertrophy were determined, which significantly improved the morphological picture of the heart compared to the control group. In the control group, the scar condition was either unchanged or worsened by the appearance of ossifications.

Discussion

Morphological analysis of the data indicated a positive effect of intra-myocardial administration of AB suspension on the altered area of the rat myocardium after cryoinjury. It was found that biomaterial particles are a chemo-attractant for macrophages, being responsible not only for their resorption but also for the possible destruction of thick collagen fibers in the scar. Macrophages localized in the area of AB implantation are producers of many cellular growth factors and cytokines, including metallo-proteinases, promoting proteolytic degradation of the inter-cellular matrix.[27] It is known that the degradation and resorption of damaged cardiac tissue, in combination with mechanical stress, can result in the formation of an aneurysm. However, the results showed that this did not

happen, since the thickness of the fibrous tissue of the left ventricular wall and the diameter of the scar remained unchanged both in the control and experimental groups. Homeostasis in the reactive zone could be determined not only by collagen but also by proteo- and glycos-aminoglycans arriving during the resorption of exogenously administered biomaterial. The latter can be synthesized by the present macrophages. The validity of this assumption has been confirmed by our previously published data.[28] Since the thickness of the fibrous tissue remained unchanged and the thickness of the muscular part of the damaged wall of the left ventricle significantly increased after the injection of AB, it can be considered that cardiomyogenesis occurred in the newly formed provisional tissue, which was formed under the influence of AB. The presence of AB promotes the formation of loose fibrous connective tissue. In addition, AB is a chemoattractant and promoter of autologous, poorly differentiated tissue-specific stem cells. At the same time, the products of AB biodegradation, together with the cellular secretomes of previous cardiomyocytes, create the prerequisites for the cardiomyogenic determination.[17] The presence of cardiac troponin I^+ in cells that were identified, as well as the presence of their binuclear forms in the peri-scar zone, is the obvious evidence of the neoplasm of cardiomyocytes and their hypertrophy.

It was previously shown that implanted AB particles initiate the migration of macrophages, resorbing them, followed by fibroblastic cells with reduced synthetic activity and the formation of a bud of blood vessel growth.[17,29] In the study, the use of AB provided the formation of vascularized, loose fibrous connective tissue. Moreover, the degree of vascularization exceeded the control group by an order of magnitude. The dynamics of vasculogenesis after AB administration indicate an early (7 days) initiation of hemocapillaries growth and their persistent stabilization throughout the observation period up to 45 days. The effect of AB in inducing hypertrophy and proliferation of cardiomyocytes in adjacent normoxic areas, promoting migration and differentiation of cardiac stem cells and progenitor cells into cardiomyocytes, or any combination of them, seems indisputable. This research showed that newly formed cardiomyocytes appeared only in the experimental group, and they were grouped in close proximity to the hemocapillaries. They were absent in the control group. Although the mechanism of cardiomyogenesis remains completely unknown, the study directly demonstrates that AB and the micro-environment it creates actually contribute to the appearance of cardiomyocytes in the area of mature cryogenic cardiosclerosis. The cardiac troponin I^+-positive cardiomyocytes observed in the area of cardiosclerosis in the study group animals may be derived from several sources, including migrating cardiomyocytes from outside of the lesion, differentiated progenitor cells, or resident cardiomyocytes with inducible proliferative activity. It is known that angiogenic factors, such as vascular endothelial growth factor-B, promote the differentiation of progenitor cells into cardiomyocytes and also induce proliferation of cardiomyocytes; therefore, it is likely that in our experiments both mechanisms are potentially important.[30] Unraveling this issue requires further research. Detailing the mechanism of renewal and induction of cardiomyogenic cells, as well as identifying the dose dependence and frequency of AB administration, would make it possible to maximize the use of this component of the regenerative effect of AB implemented on the heart muscle.

The AB implanted into the zone of formed cryogenic cardiosclerosis was subjected to the gradual resorption by macrophages and replaced by regeneration from fibrous connective and muscle tissue, represented by vascularized loose fibrous connective tissue and cardiomyocytes grouped in the form of separate clusters.

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Conflict of interest

The authors declare no obvious or potential conflicts of interest related to the publication of this article.

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