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The Influence of Titanium Coating of Mesh Polypropylene Endoprostheses on Their Biocompatibility

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Abstract—A comparative analysis of the proliferative activity of inflammatory infiltrate cells and the distribution of collagen type I and III in granulomas formed in the area of contact of mesh materials made of polypropylene (PP Std Light) and titanium-coated polypropylene (TiMesh) was performed via polarized microscopy and immunohistochemical detection of Ki-67 protein. Mesh materials were implanted in the soft tissues of the lumbar region of rats. The number of proliferative cells around implants made of the standard polypropylene (PP Std Light) 7 days after the operation was detected with the use of antibodies to Ki-67 protein to be less than the number of those around titanium-coated polypropylene (TiMesh) (29.1 ± 5.7 and 33.6 ± 3.1%, respectively, $p < 0.001$). The similar differences were revealed 1 month after the beginning of the experiment (15.9 ± 4.3 and 26.9 ± 3.6%, respectively, $p < 0.001$). Various types of collagen fibers in granulomas around the implanted mesh materials were detected in polarized light with the use of sections stained with Sirius Red. The ratios between collagen fibers type I and III in granulomas around PP Std Light and TiMesh materials determined 7 days after the operation were 1.085 ± 0.022 and above 1.107 ± 0.013, respectively ($p = 0.017$). The ratio increased to 1.174 ± 0.036 and 1.246 ± 0.102, respectively ($p = 0.045$) 1 month after the operation. The obtained results suggest that the titanium coating of polypropylene stimulates the formation of collagen type I and more mature connective tissue around mesh endoprostheses.

Keywords: mesh materials, polypropylene, titanium-coated polypropylene, Ki-67, collagen type I and III

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INTRODUCTION

Despite the recent satisfactory results of the use of synthetic mesh endoprostheses, their long-term conflicts with the body tissues are often described in the literature. This phenomenon consists in a nagging aseptic inflammation leading to discomfort, chronic pain, or even rejection of materials (Parshikov et al., 2011b). One way to increase the biocompatibility of mesh endoprostheses is the development of titanium-containing mesh materials in which titanium or compounds thereof play a role of the endoprosthesis surface in contact with the surrounding body tissues (Chernov et al., 2012; Sarbaeva et al., 2013). Titanium endoprostheses or titanium-coated mesh polypropylene implants are the most common materials of this group (Parshikov et al., 2011a; Schopf et al., 2011; Kolpakov and Kazantsev, 2015).

However, the problem of the biological influence of foreign materials on tissues still remains open. A number of researchers have noted favorable effects of mesh implants in tissues under the conditions of weak inflammatory reaction with the use of inhibitors of mast cell degranulation (Orenstein et al., 2010). It was also proposed to increase the biocompatibility with tissues by using mesh endoprostheses containing thin filaments and large pores in order to reduce the inflammatory response intensity (Orenstein et al., 2012). This circumstance was due to the fact that pronounced inflammatory response to a foreign body leads to a reduction of the collagen formation and a low integration of mesh materials in tissues (Pascual et al., 2012). The data of other researchers indicated that a more pronounced inflammatory response provides a stronger interaction of implant with tissues (Pereira-Lucena et al., 2010, 2014; Ivanov et al., 2012). Thereby, there is a question regarding the relationship between the inflammatory response intensity and the mature collagen formation. Various parameters are used to evaluate the tissue response including the morphological features of granulomas (Klinge et al., 2014), the number of macrophages (Garcia-Moreno

et al., 2015), the content of biologically active compounds, the proliferative activity of cells (Jacob et al., 2012; Müller-Stich et al., 2014), and the expression of genes of inflammatory cytokines and growth factors (Asarias et al., 2011).

A clear relationship has been observed between the character of the inflammatory process and the presence of the connective tissue around a mesh material (Klolsterhalfen and Klinge, 2013), with collagen being a main component of the connective tissue scar. In such cases, dense mature collagen type I or immature collagen type III was formed (Garcia-Moreno et al., 2015). A ratio between collagen type I and III of greater than 3 shows successful formation of the connective tissue. Klosterhalfen and Klinge (Klosterhalfen and Klinge, 2013) have examined 623 clinical complications caused by mesh endoprostheses via the immunohistochemistry method and found a reduction of the above ratio in the connective tissue in 70% of cases, this indicating an interruption of the wound healing process. The ratio between various collagen types formed after implantation of various mesh materials can also be studied by polarized light microscopy with Sirius Red staining (Junqueira et al., 1978; Pascual et al., 2015).

The goal of the present study is to evaluate the proliferative activity of inflammatory infiltrate cells in the area of implantation of mesh materials made of polypropylene and titanium-coated polypropylene with the use of the immunohistochemistry method and characterize the collagen types in the formed connective tissue by polarized microscopy of tissues stained with Sirius Red.

MATERIALS AND METHODS

Mesh materials of 1.5 × 1.5 cm in size were implanted in the soft tissues of the lumbar region of 20 outbred white 250-g rats of both sexes. The study was performed according to the ethical principles established by the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes accepted in Strasbourg, March 18, 1986, and confirmed in Strasbourg, June 15, 2006.

Operations ($n = 20$) were performed under general anesthesia with Nembutal (intraperitoneally, 30 mg kg^{-1}). Meshes made of standard polypropylene (PP Std Light, a mesh thickness of 380 μm, a thread of 90 μm, and a specific weight of 62 g m^{-2}) and those made of polypropylene containing a thin titanium layer deposited on the surface via the plasma-activated chemical vapor deposition (PACVD) technology (TiMesh, a thickness of 300 μm, a thread of 90 μm and a specific weight of 35 g m^{-2}) were used in the first group (ten animals) and the second group (ten animals), respectively.

The animals (five rats with PP Std Light and five rats with TiMesh) were taken out from the experiment by air embolism (7 mL kg^{-1}) under general anesthesia with intramuscularly administered Xylazine (2 mg kg^{-1}) and Zoletil (8 mg kg^{-1}) 7 days and 1 month after the operation. The implants were removed by dissecting the skin and the adjacent soft tissues at a distance of 1–2 cm from the implant edge.

The frontal tissue sections with attached mesh materials were fixed in 10% buffered formalin (pH 7.4) for 24 h and embedded in wax (melting point of 54°C) by processing with the use of an STP 120 Spin Tissue Processor (Thermo Scientific) and an EC-350 embedding station (Thermo Scientific). Serial sections of 5-μm thickness were then prepared, automatically stained with hematoxylin and eosin on a Microm HMS 740 instrument (Thermo Scientific), and placed into a Bio-Mount medium (Bio Optica Milano S.P.A., Italy).

Immunohistochemical examinations of mesh materials were carried out according to a standard protocol. Serial sections of 5-μm thickness were prepared from the blocks for histology with the use of a microtome followed by their mounting on glass slides coated with poly-L-lysine. The sections were dewaxed, and their antigenic activity was recovered in a PT module at 98°C for 20 min. The further procedures were performed in automatic mode on an Autostainer 360 with the use of the QUANTO visualization system. The protocol used in the Autostainer included the treatment of sections with H_2O_2 for 10 min, the protein blocking for 10 min, the treatment with the primary (for 30 min) and secondary (for 10 min) antibodies, DAB (for 5 min), and washing with Tris buffer (pH 6) containing Tween 20.

One hundred microliters of rabbit anti-Ki-67 monoclonal antibody (SP 6 EPITOMICS at 1 : 100 dilution) used as a primary one were applied to sections. Horseradish peroxidase-conjugated donkey antibody to rabbit immunoglobulin (EPITOMICS) was used as a secondary antibody.

After incubation, the sections were washed out with distilled water followed by final staining with Mayer's Hematoxylin for 3 min. Once the sections were stained blue, the glass slides were taken out, followed by stepwise dehydration in increasing concentrations of ethanol, and placed into a Bio-Mount medium (Bio Optica Milano S.P.A., Italy). The preparations were examined in a microscope (Axioplan 2 imaging, Carl Zeiss) with photofixation (AxioCamERc 5s). The percentage of nuclei of proliferative cells stained brown with diaminobenzidine of the total number of nuclei in the area of contact of mesh materials with the connective tissue was calculated in immunohistochemical studies.

A Picro Sirius Red Stain Kit for staining the connective tissue was used for staining with Sirius Red. Sections of 5-μm thickness were placed into a Picro

Sirius solution (0.1% solution of Sirius Red F3BA containing picric acid, pH 2) for 30 min, washed out with 0.01 N HCl for 2 min, dehydrated, and embedded in a Bio-Mount synthetic mounting medium (Bio Optica Milano S.P.A., Italy).

Collagen type I and III were visualized in a polarized light within 0.1 mm^2 area around the mesh material filaments at a lens magnification of 40×, with each area being studied about three times. The color histograms of the percentage distribution of red, green, and blue pixels were examined, and the ratio between red and green pixels corresponding to the distribution of collagen type I and III was determined in each case.

The results were quantitatively evaluated via morphometric studies. The measurements were performed with the use of the ImageJ 1.46 software (Wayne Rasband, National Institutes of Health, United States), the normality of the data distribution was estimated by the Shapiro–Wilk test (via the *W*-criterion), and the significance of differences between the normally distributed sets of quantitative data was determined by Student's *t*-test with the use of the STATISTICA 10.0 software in Windows 7 OS. The average values and the standard deviations of the data sets are given in this paper, with the differences being considered statistically significant at $p < 0.05$.

RESULTS

Morphological studies show the formation of foreign-body granulomas around the mesh material filaments, with their characteristics depending on the structure of examined materials and the duration of the experiment. The granulomatous inflammation of macrophages, lymphocytes, and foreign-body giant cells in the area of contact of mesh materials with tissue indicates the presence of chronic inflammation. Micrographs of foreign-body granulomas around the filaments of various mesh materials formed 7 days and 1 month after the beginning of the experiment are given in Figs. 1a–1d. A large number of foreign-body giant cells around the TiMesh implant observed after 7 days and 1 month should be noted.

The development of chronic inflammatory response was accompanied by cell proliferation around mesh materials. The proliferative activity of cells was investigated via immunohistochemical staining of Ki-67 protein with monoclonal antibody.

Figures 1e and 1f show the results of immunohistochemical detection of proliferatively active cells (brown nuclei) in the granulomatous inflammation around the elements of various mesh implants 7 days after implantation. Quantitative analysis reveals significant differences ($p < 0.001$) between the percentage of proliferative cells around the polypropylene mesh elements (29.1 ± 5.7%) and that in infiltrates around TiMesh elements (33.6 ± 3.1%).

Less pronounced cell proliferation is observed in the area of contact of mesh materials with connective tissue 1 month after implantation of the material into animal tissues. Micrographs of foreign-body granulomas around the elements of PP Std Light and TiMesh implants detected 1 month after implantation are shown in Figs. 1g and 1h, and indicate the brown nuclei of proliferative cells. The content of proliferative cells in granulomas around the elements of polypropylene mesh was determined via quantitative analysis to be less than that in infiltrates around TiMesh, namely, 15.9 ± 4.3 and 26.9 ± 3.6%, respectively (the differences were significant at $p < 0.001$).

The proliferative activity of cells around PP Std Light mesh material is significantly reduced from 29.1 ± 5.7 to 15.9 ± 4.3% ($p < 0.0001$) within the period from the 7th to the 30th day of the experiment. The same trend is observed in the case of the inflammatory response around TiMesh (from 33.6 ± 3.1 to 26.9 ± 3.6% at $p < 0.0002$). Thus, greater reduction of the proliferative response around PP Std Light material is detected.

Morphological study of granulomas 7 days after the operation reveals the granulation tissue growth along with the weakly pronounced fibrous connective tissue components. Coarse collagen fibers were actually not found by optical microscopy of samples stained with Sirius Red to occur in granulomas around PP Std Light (Fig. 2a) and TiMesh (Fig. 2b) materials in the areas where they were in contact with tissues. Light microscopy of tissue samples stained with Sirius Red performed 1 month after the beginning of the experiment reveals red collagen fibers in the interface area in granulomas around PP Std Light (Fig. 2c) and TiMesh (Fig. 2d) materials.

The content of various collagen fiber types in granulomas around mesh materials 7 days after implantation was quantitatively analyzed in sections stained with Sirius Red under polarized light. A faint greenish color around mesh materials observed in this study of tissue samples indicates the beginning of the formation of immature collagen type III. Dark red and yellow colors of collagen fibers around mesh materials correspond to the mature collagen fibers out of the contact area between mesh materials and tissue. A homogeneous bluish color (Figs. 2e, 2f) corresponds to the polypropylene particles of mesh materials. The ratios between collagen fibers type I and III occurring in the interface areas were determined in granulomas around PP Std Light and TiMesh materials 7 days after the operation to be 1.085 ± 0.022 and 1.107 ± 0.013, respectively, thus being significantly higher in the case of the latter ($p = 0.017$).

A study of the samples of Sirius Red-stained sections of tissues around mesh materials under polarized light 1 month after implantation shows the presence of collagen fibers in the granulomas of the interface area around both PP Std Light (Fig. 2g) and TiMesh

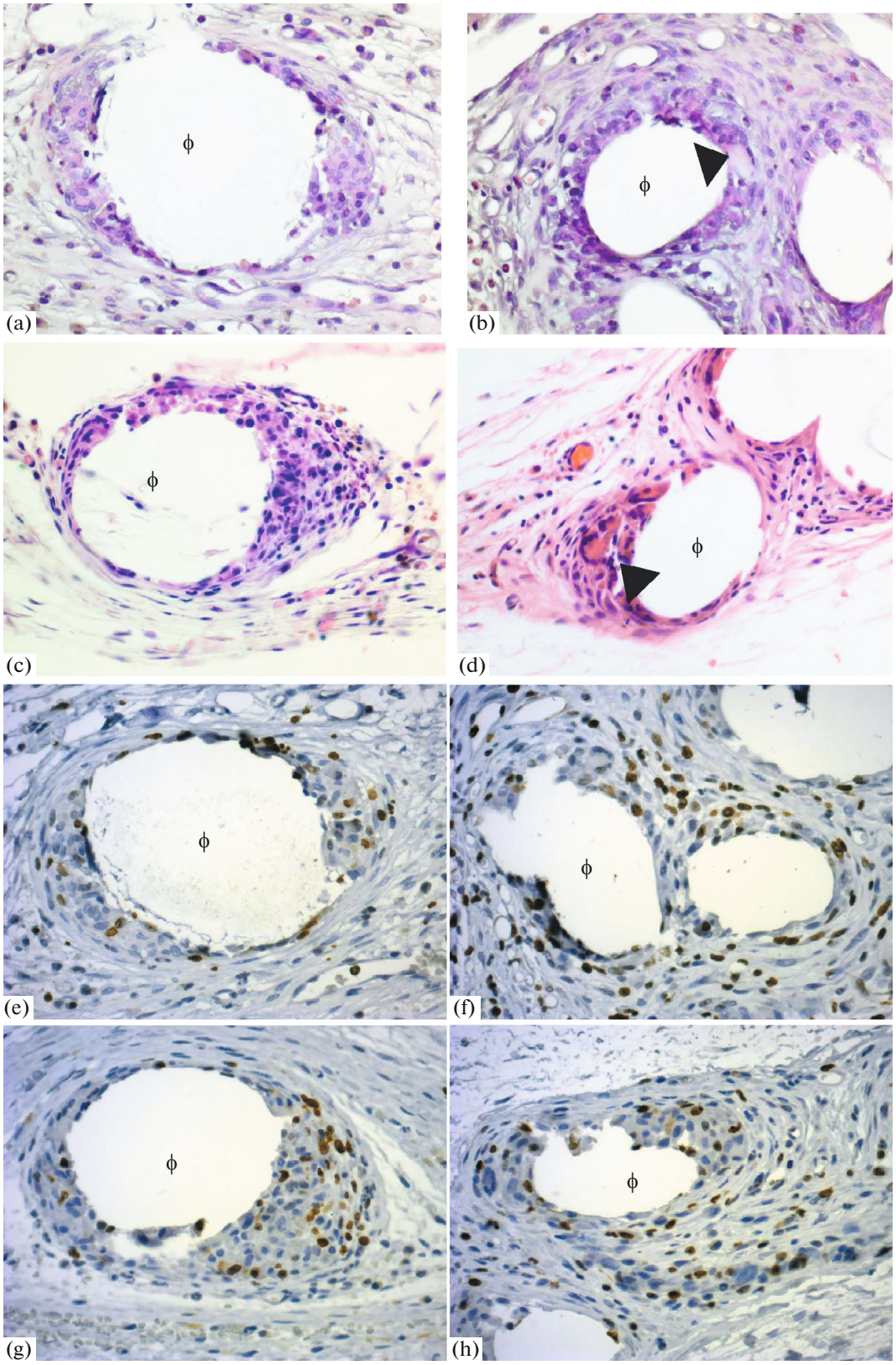

Fig. 1. (a–d) General views (a magnification of 40×) of hematoxylin and eosin-stained foreign-body granulomas around (a, c, e, g) PP Std Light polypropylene and (b, d, f, h) titanium-coated TiMesh polypropylene filaments (a, b, e, f) 7 days and (c, d, g, h) 1 month after the beginning of the experiment, indicating (b, d) a large number of foreign-body giant cells (arrow ends) around the filaments (ϕ) of TiMesh implant. (e–h) Detection of proliferative cells of foreign-body granulomas by immunohistochemical reaction with anti-Ki-67 antibody after staining with DAB/Mayer's Hematoxylin, indicating a smaller number of proliferative cells (brown nuclei) in granulomas around the elements of (e, g) polypropylene mesh than (f, h) in infiltrates around TiMesh (a magfnification of 40×).

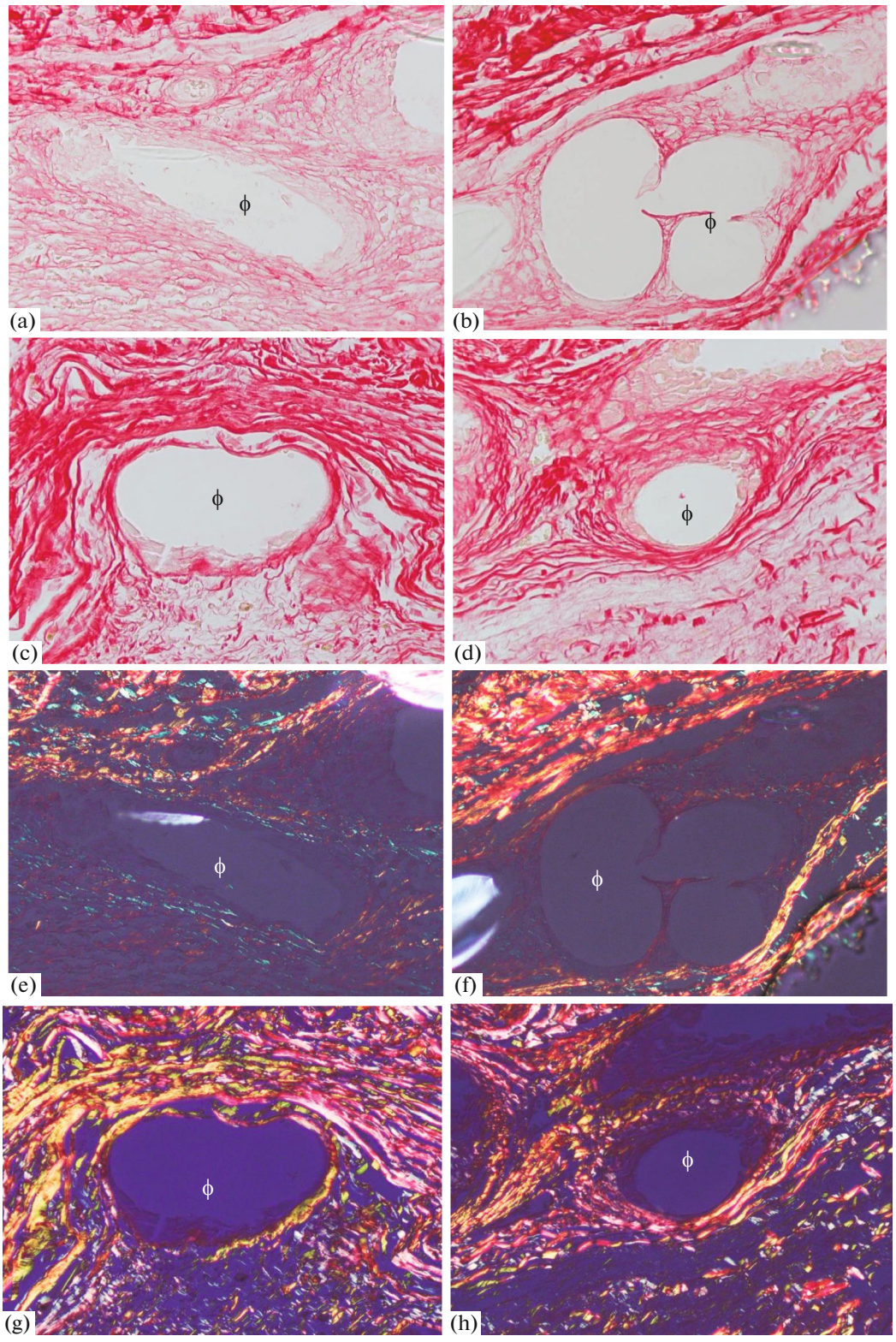

Fig. 2. Detection of collagen in foreign-body granulomas around (a, c, e, g) PP Std Light polypropylene and (b, d, f, h) titanium-coated TiMesh polypropylene filaments (a, b, e, f) 7 days and (c, d, g, h) 1 month after the beginning of the experiment by (a–d) light microscopy and (e–h) polarized light microscopy of sections stained with Sirius Red, indicating that mature collagen fibers (red color) appear around mesh filaments (ϕ) only 1 month after the beginning of the experiment (a magnification of 40×).

(Fig. 2h) materials. However, the collagen fibers around PP Std Light mesh material are mostly green, which indicates the formation of immature collagen type III. The ratio between the collagen fibers type I and III observed in the granulomas of the interface area around PP Std Light mesh material 1 month after the operation is 1.174 ± 0.036, while that determined in the case of TiMesh material is significantly higher, namely, 1.246 ± 0.102 ($p = 0.045$).

The higher the content of collagen type I in comparison to collagen type III around TiMesh implants, the more active the formation of mature collagen type I. It should be noted that a significant increase in the relative content of mature collagen type I is observed in granulomas around PP Std Light and TiMesh materials within the period from the 7th to the 30th day after the operation.

DISCUSSION

Mesh materials, mostly synthetic ones, are currently widely used in various fields of medicine, in particular to strengthen the anterior abdominal wall at hernias (Grigoryuk and Kovalev, 2010; Shcherbatykh et al., 2010). There are a large number of research studies that use histological methods, scanning electron microscopy and immunohistochemistry to evaluate the efficacy of mesh materials (Naumov et al., 2010; Ivanov et al., 2012).

A synthetic mesh undergoes changes (degradation of the polymer structure is observed) typical of any foreign body after implantation in the abdominal wall. Various complications are noted in such operations due to the interactions between tissues and mesh materials. The main complications are recovery of the abdominal wall defect because of the mesh contraction or its incomplete integration into the body tissues or the penetration of mesh materials in the internal organs or to the skin surface and the formation of acute purulent inflammation around the materials (Timerbulatov et al., 2013). To prevent these complications, the characteristics of various mesh materials should be studied in animal experiments that use histological methods, making it possible to evaluate the cell response to mesh materials as foreign bodies (Romanov et al., 2012).

The implantation of synthetic mesh materials activates neutrophils, lymphocytes, macrophages, and foreign-body giant cells (Ivanov et al., 2012). These cells secrete various enzymes degrading the material structure and surround a foreign body. Lymphocytes and foreign-body giant cells produce a large number of free radicals stimulating the connective tissue growth. Eventually, these processes lead to the formation of dense stationary lesion in the anterior abdominal wall tissue around mesh materials. These phenomena may be a basis of various complications (Parshikov et al., 2013; Pikalyuk et al., 2014).

The modern reconstructive surgery deals with physically and chemically inert mesh implants, however, the implantation of any foreign body in tissues leads to the development of a protective immune response. The mesh elements are completely encapsulated because of the formation of granulomas containing proliferative cells and extracellular matrix. The cells that migrate to the contact area between mesh material and tissue participate in the formation of the connective tissue capsule isolating the mesh material from the surrounding tissues. It has been shown that macrophages, lymphocytes, neutrophils, mast cells, and foreign-body giant cells are components of the inflammatory infiltrate (Klinge et al., 2014).

The proliferative and synthetic activity of inflammatory infiltrate cells is responsible for forming extracellular matrix, including collagen. Cytokines are known to be main regulators of cell proliferation and synthesis of extracellular matrix and collagen. Cytokines are synthesized in the damaged tissue, modulate the inflammatory cascade during the first phase of the inflammatory response, and initiate the regenerative processes in the abdominal wall (Dubay et al., 2004).

There exists a direct correlation between the inflammation and the connective tissue formation around the implanted mesh material (Laschke et al., 2009). The introduction of mesh materials into tissues significantly changes the processes of collagen formation. Immature collagen type III is quickly replaced by mature collagen type I during wound healing, but this process may be considerably slowed down because of the introduction of mesh material (Brown and Finch, 2010). As a result, a decrease in the ratio between collagen type I and III is observed, this leading to a disruption of the mechanical stability of mesh materials (Junge et al., 2004; Klosterhalfen et al., 2005). The influence of implantation on the ratio between various collagen types may strongly depend on the used type of mesh material.

Comparative studies of VEGF and COX2 proinflammatory factors in tissues and the collagen formation processes around mesh materials made of polypropylene and titanium-coated polypropylene have been performed (Pereira-Lucena et al., 2014). These authors found that the inflammatory response was weaker and the collagen formation was more pronounced 7 and 40 days after implantation of polypropylene mesh material in the abdominal wall of rats in comparison to the use of titanium-coated polypropylene. A tendency toward a decrease in the expression of VEGF and COX2 and the synthesis of mature collagen was observed in all animal groups from the 7th to the 40th day of the experiment. Thereby, a reduction of the inflammatory response activity in tissues within this period resulted in a decrease in the mature collagen formation.

The study in domestic pigs has shown that the polypropylene mesh contracted due to a pronounced

inflammatory response and the formation of the scar tissue (Scheidbach et al., 2004), whereas titanium-coated polypropylene deformed less due to smaller volumes of inflammatory foreign-body granulomas (14.9 vs. 8.8%, respectively, $p < 0.05$). Thus, more pronounced inflammatory response was accompanied by more intense formation of fibrous tissue.

Ki-67 protein is a universal cell proliferation marker, since it is detected in cells during all phases of mitosis except for G0 (Hofmann and Bucher, 1995). Therefore, the examination of the features of Ki-67 distribution makes it possible to quantify the percentage of proliferatively active cells in granulomas. A smaller percentage of proliferative cells determined by Ki-67 expression was observed around titanium-coated polypropylene in comparison to polypropylene without the coating (15 and 21%, respectively); however, these differences were not significant (Scheidbach et al., 2004).

In the present study, a significantly higher proliferative activity of cells around titanium-coated polypropylene mesh (TiMesh) than that around conventional polypropylene (PP Std Light) is found, with these differences being observed both 7 days and 1 month after the beginning of the experiment. The proliferative activity of cells around PP Std Light mesh material is significantly reduced within the period from the 7th to the 30th day of the experiment. The same trend is observed in the case of the inflammatory response around TiMesh, with a decrease in the proliferative response around PP Std Light being more pronounced.

The obtained data clearly show that the proliferative activity of cells in foreign-body granulomas formed in the interface area is an appropriate criterion to evaluate not only the dynamics of the proliferation process, but also the intensity of the inflammatory response depending on the physical and chemical properties of used materials.

The differences in the proliferative activities of cells in the area of contact of mesh materials with tissue seem to bring about differences in the collagen formation processes. The ratio between collagen type I and III is lower in the area characterized by low proliferative response around PP Std Light material than in the area around TiMesh material. These differences are retained for 1 month after the beginning of the experiment, despite a significant increase in the percentage of mature collagen type I by that time.

Thereby, a high proliferative activity of cells around mesh materials contributes to the rapid formation of mature collagen type I, providing better integration of implant in tissues.

The evaluation of the effect of polypropylene titanium coating makes it possible to claim that the coating promotes the formation of collagen type I and more mature connective tissue around mesh endoprostheses.

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