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*Cellular and Molecular Biology*

# Comparative immunohistochemical study of tissue integration of macroporous and laminar surgical meshes

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**Summary.** Intraperitoneal surgical mesh implantation is required for laparoscopic ventral hernia repair. Composite meshes are well known in animal models and human practice. The aim of our study is to compare the biological behaviour of two different textured silicone-covered polypropylene meshes.

Transmural abdominal wall defect was created in 40 rabbits and treated as follows: In 20 animals a polypropylene mesh with a laminar silicone covering (LSPP) and in the rest a macroporous textured mesh knitted of silicone-impregnated polypropylene filaments (MSPP) was applied. One and three weeks after implantation we evaluated the intraperitoneal adhesion formation of the mesh macroscopically, histologically and immunohistochemically to detect the reactive cells, especially inflammatory, endothelial and mesothelial cells, as well as their proliferative activity, and with Scanning Electron microscopy to visualize the surface of the meshes.

The adhesion formation caused by the composites showed no statistical difference after one week although in the three weeks old samples the LSPP adhesion was significantly weaker than that of MSPP. As complications, serome formation in both groups, fistulas, abscesses, and sc. haematoma in the LSPP group were found. Only in MSPP containing tissues was the decrease of Ki-67 positive proliferating cells significant. A significant increase in VEGF expressing cells was observed only in MSPP containing three week old samples, suggesting better regulation of vascular growth in tissues surrounding the implants. In one week old specimens we observed an irregular proliferation of cytokeratin containing mesothelial cells in both group. The intraperitoneal surface of MSPP mesh was covered with neoperitoneum, while it was not regurarly seen on LSPP mesh after three week.

**Key words:** Intraperitoneal adhesions, Mesh, Cell proliferation, Cytokeratin

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## Introduction

Hernia surgery is one of the most common general surgical procedures performed globally. Tension free – mesh implantation became the gold standard in abdominal wall reconstruction. It is estimated that worldwide approximately 1 million meshes are implanted yearly (Offner, 2004).

Different animal studies, including small animals (rats, rabbits), and large animals (porcine) supports a tendency towards fewer adhesions when using composite meshes or expanded polytetrafluoroethylene (ePTFE) for laparoscopic ventral hernia repai. Harrel et al. (2006) implanted 4x4 cm pieces of mesh in 30 rabbits and adhesion formation was assessed after 1, 4, 8 and 16 weeks with sequential laparoscopy. DualMesh® had significantly less adhesions than Proceed®, Composix® and Marlex® at all investigated times. There were no differences in adhesions between Proceed® and Composix® mesh. Another newly published study in rabbits showed significantly lower adhesion degrees with Proceed® and ePTFE mesh compared with Mersilene®, Prolene®, and Vypro® mesh at 4 weeks post implantation (Kiudelis et al., 2007).

The macroporous nature of the hernia meshes is

thought to be responsible for the excellent tissue ingrowth. Rosen reports (2009) a study of 109 patients with ventral hernia, repaired with polyesther based meshes. He interprets his outstanding results and the successful treatment of the wound infection with the macroporous nature of the mesh.

The majority of tissue ingrowth and strength take place within 2 weeks after mesh implantation and thereafter increase slowly until 3 months postoperatively (Majercik et al., 2006) The biological response to hernia meshes can be characterised morphologically by the formation of collagenous tissue, inflammation, foreign body reaction, neoperitoneum formation and neovascularization. The tissue response depends on the material and the pore size of the surgical mesh (Greenawalt et al., 2000; Klinge et al., 2002).

Different experimental studies have shown the superiority of polypropylene (PP) meshes to all other mesh material regarding strength of ingrowth to the surrounding tissue (Bellon et al., 1996). It has been documented that ePTFE materials have a tendency to encapsulate instead of being integrated into the host abdominal wall (Bujan et al., 1997).

The laminar layered silicone covered PP mesh (LSPP – Laminar Silicone layer on the PP mesh) and a silicone impregnated polypropylene mesh (MSPP – Macroporous Silicone layer on the PP mesh) were compared.

To detect the inflammatory reactions and wound healing activity Ki-67 antibody was used. This is the prototypic cell cycle related nuclear protein, expressed by proliferating cells in all phases of the active cell cycle (G1, S, G2 and M phase). Monoclonal Anti-Proliferating Cell Protein Ki-67 reacts with the Ki-67 nuclear antigen.

To assess vessel proliferation, Vascular Endothelial Growth Factor (VEGF) was applied. VEGF is a homodimeric, disulfide-linked glycoprotein involved in angiogenesis. It exhibits potent mitogenic and permeability inducing properties specific for the vascular endothelium. Of the four isoforms of VEGF, the smaller two, VEGF 165 and VEGF 121, are secreted proteins and act as diffusible agents, whereas the larger two (VEGF 189 and VEGF 206) remain cell associated.

Cytokeratins, a group of at least 29 different proteins, are characteristic of epithelial and trichocytic cells. This antibody recognizes keratin polypeptide of 45, 46 and 56.5 kDa. Cytokeratin 6 (56 kDa) is a "hyperproliferation" cytokeratin expressed in tissues with natural or pathological high turnover.

We have evaluated the mesh induced intraperitoneal adhesion formation macroscopically and morphologically. For better understanding of the biological behaviour of the prostheses immunohistochemistry was used to complete the investigations.

## Materials and methods

LSPP (Sil Promesh®; Surgical-IOC Company, France; Fig. 1.) is a dual-sided, macro perforated, non-woven, polypropylene mesh, with a non adherent silicone covering on the intraperitoneal side, for open and laparoscopic hernia repair. Features: size: SI.3030MO-2S: 30x30 cm; gross weight: 0.4 kg.

The MSPP consists of PPKM403 polypropylene mesh (TDA Textile Development Associates, Inc. USA), which is a knitted polypropylene mesh with a pore size: 1.3x1 mm, weighing 45 g/m$^2$ and it is 0.43 mm thick. For the silicone covering the NuSil MED-6215 (Polytech Pt., Germany) was used which is a two component silicone elastomer (See Fig. 2). After impregnation, all the meshes were sterilized by Sterrad autoclave (Central Sterilizing Labour, University of Pécs, Hungary).


**Fig. 1.** LSPP: the multifilament polypropylene mesh (signed with circle around the fibres) with smooth silicone layer (arrowed).

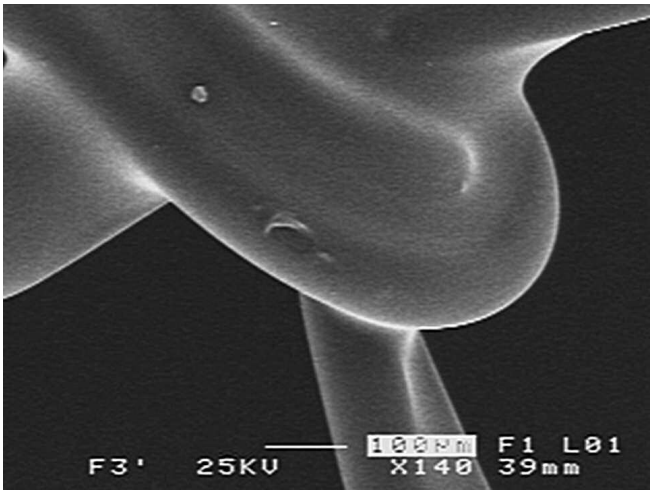


**Fig. 2.** MSPP: silicone covered polypropylene filaments of the mesh.

*Experimental protocol*

A total of 40 New Zealand White rabbits (weighing 2.05-3.1 kg ~ 2.576 kg) were used in this study. The animal experiment was in accordance to rules and regulations regarding the use of animals in medical research, and the study was approved by the Committee on Animal Research of Pécs University (BA02/2000-1/2004).

All animals were allowed to acclimate for at least a week prior to surgery. The animals were given rabbit chow and water *ad libitum* during the acclimatization period and throughout the rest of the study except the day of surgery. The animals were not allowed to eat and drink 12 hours before the operation, and they were not fed postoperatively for 24 hours.

The animals were anaesthetized with intramuscular ketamine hydrochloride (200 mg), after premedication with diazepam (10 mg).

After the total abdomen was shaved and disinfected (Betadine), a 10 cm long vertical midline skin incision was carried out under sterile conditions, and a 3x4 cm big full thickness abdominal wall defect was made in the lower part of the abdomen by excision of all the abdominal layers including the peritoneum. It was covered with a 4x5 cm sized silicone covered polypropylene mesh, and fixed with running sutures (Prolene® 4/0, Johnson & Johnson Medical Ltd. Gargrave, United Kingdom). The skin and subcutaneous tissues were also closed with running sutures (Vicryl Rapid® 2/0, Johnson & Johnson Medical Ltd.).

Animals were daily checked for complications

The rabbits were sacrificed 7 and 21 days after surgery. The animals were euthanized with an overdose of potassium injection. The skin was carefully removed, then the presence of fluid collection, infection, erosion or other signs of rejection were noted. Then almost the entire anterior abdominal wall was resected 'en bloc', including the implanted mesh, the underlying visceral adhesions if present and a 1-cm border of neighbouring native tissue. During resection, the presence of adhesions was quantified by extent which was scored by area (%) of the implant surface covered by adhesions.

*Morphological investigations*

HE staining was used to quantify foreign body giant cells, polymorpho-nuclear and mono-nuclear reactive cells and neo-formed vessels, as well as to supervise the blocks before immunohistochemistry.

For immunohistochemical quantification of proliferating cells, the Ki-67-specific mouse monoclonal antibody was used (clone: B56, dilution: 1:200, source: Histopathology Ltd., Pécs, Hungary). The proportion of Ki-67-positive cells was determined on tissue sections x40 magnification and the proliferative index was presented on diagrams. The Ki-67 reactive cells appeared as clusters of brown pigment within both mononuclear and multinuclear populations of cells that tended to encase the implanted materials (Fig. 3A).

To assess vessel proliferation, Vascular Endothelial Growth Factor (VEGF) specific mouse monoclonal antibody (clone: JH121, dilution: 1:200, source: Thermo Fisher Scientific/Lab Vision Corporation, Fremont, California, USA) was applied. This was a red granular cytoplasm signal (Fig. 3/B) representing those cells which produce this growth factor, mostly in the same locations as proliferating cells. Our scoring criteria are presented in Table 1.

The MNF 116 broad spectrum cytokeratin (CK) specific mouse monoclonal antibody (clone: MNF 116, dilution: 1:200, source: Histopathology Ltd.) was used to

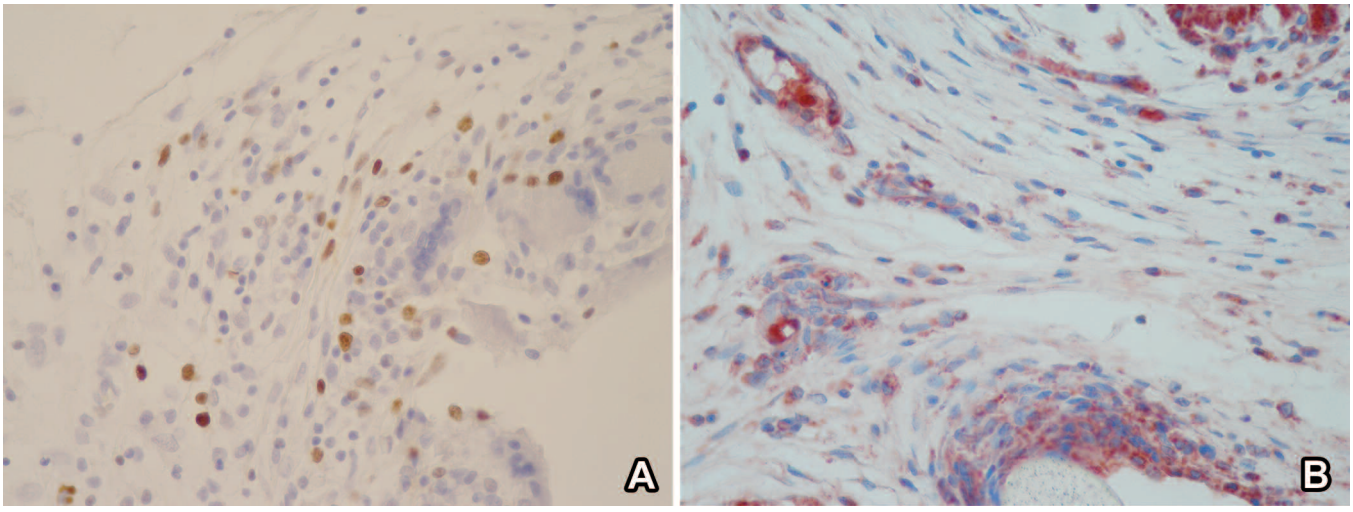


**Fig. 3. A.** Positive staining for Ki-67. **B.** Positive staining for VEGF. x 40

detect the formation of mesothel over the visceral side of prostheses. This antibody recognizes keratin polypeptide of 45, 46 and 56.5 kDa. It is an orange coloured cytoplasmatic signal.

After the sections were deparaffinized and rehydrated, then treated with Heat Inducted Antigen Retrieval procedure using citrate buffer (10 mM, pH= 6, source: Histopathology Ltd.) for 5 minutes in case of VEGF and CK and 15 minutes for the Ki-67, in

**Table 1.** Scoring criteria for the immunohistochemical analysis of VEGF presence.

| score | VEGF positive cells |
|---|---|
| 0 | No or rare positive cell |
| 1 | <20% positive cells/x40 field |
| 2 | 20-60% positive cells/x40 field |
| 3 | 60%< positive cells/x40 field |

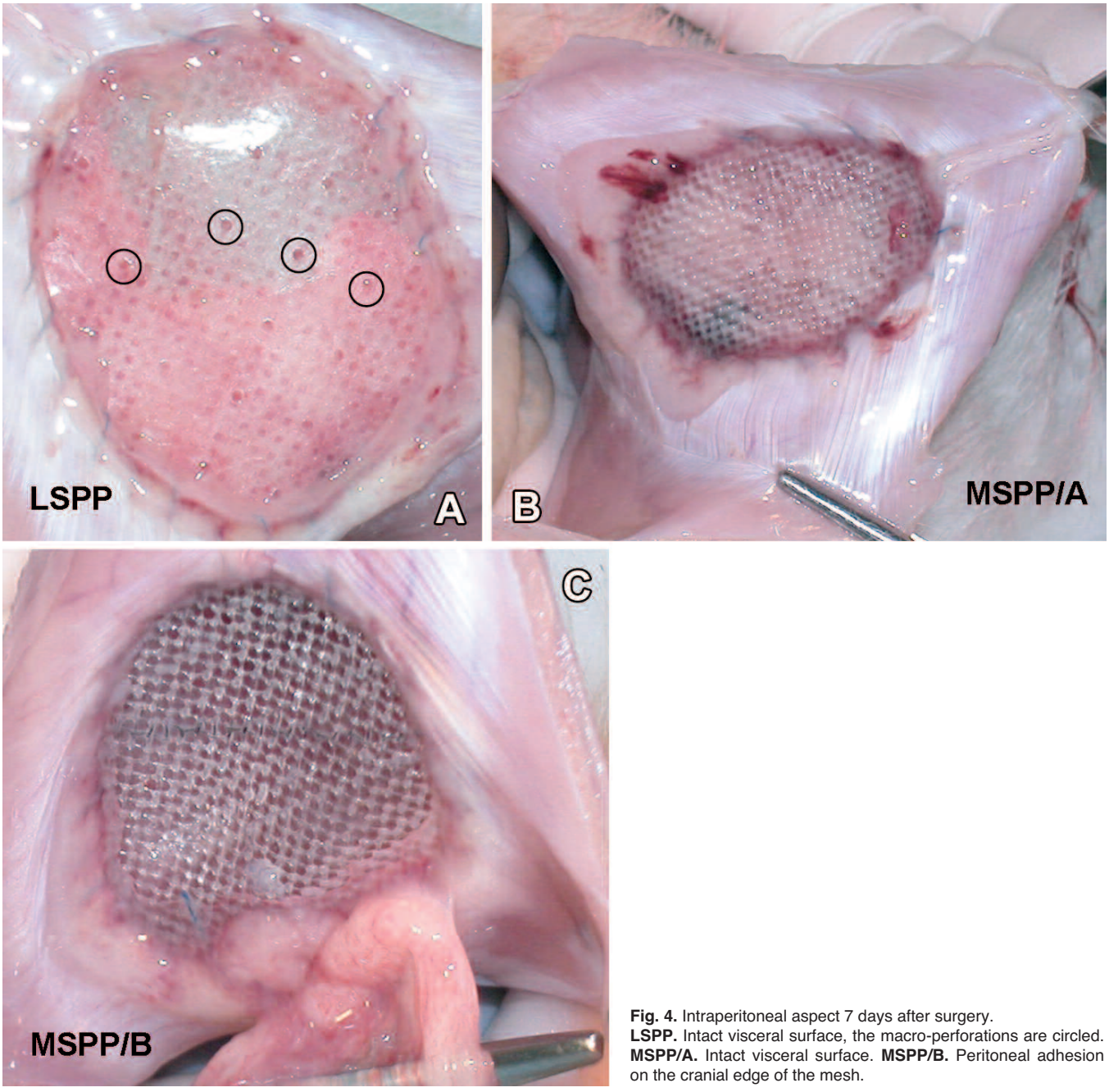


**Fig. 4.** Intraperitoneal aspect 7 days after surgery. **LSPP.** Intact visceral surface, the macro-perforations are circled. **MSPP/A.** Intact visceral surface. **MSPP/B.** Peritoneal adhesion on the cranial edge of the mesh.

microwave oven (P= 750 W, Whirlpool), then incubated with primary antibodies for 60 minutes at room temperature. The secondary antibody, the biotinylated goat anti-mouse immunoglobulin (dilution. 1:100, source: Becton Dickinson, California, USA) was incubated for 30 minutes on the slides. Then peroxidase-conjugated Streptavidin (dilution: 1:500, Source: Becton Dickinson) was used for 30 minutes. To detect peroxidase activity, for the nuclear Ki-67 location, the 3,3 Diaminobenzidine tetrahydrochlorid (DAB, Thermo Fisher Scientific/Lab Vision Corporation) and for membrane/cytoplasmic location of antigens (VEGF, CK), 3amino-9ethyl-carbazole (solvent-resistant AEC, Histopathology Ltd.) were used as chromogens with the substrate $H_2O_2$. After each step, sections were washed in TBS (pH=7.6, source: Histopathology Ltd.) for 3x5 minutes. The slides were counterstained with haematoxylin for 15 seconds, dehydrated and mounted with Pertex (Szkarabeusz, Pécs, Hungary).

### *Scanning electron microscopy*

For SEM evaluation the specimens were fixed in a mixture of 2% formaldehyde and 2.5% glutare solution for 24 hours. The samples were thereafter carefully washed 3 times in phosphate buffer and dehydrated in increasing concentrations of alcohol. After the dehydration with absolute alcohol for 20 minutes was finished, the samples were mounted on the worksheet and coated with gold ("4 9"- fine gold) and analyzed with electron microscope (JEOL, JSM 6300 Scanning Microscope, Japan).

### *Statistical analysis*

Statistical evaluation was performed using SPSS 15.0 statistical program for Windows. The results were presented as mean values and standard error. The cell proliferation was analysed using Student unpaired t-test, to determine significance levels showing statistical significance p values of less than 0.05, while in the case of VEGF analysis the Mann-Whitney test was used ($p<0.01$).

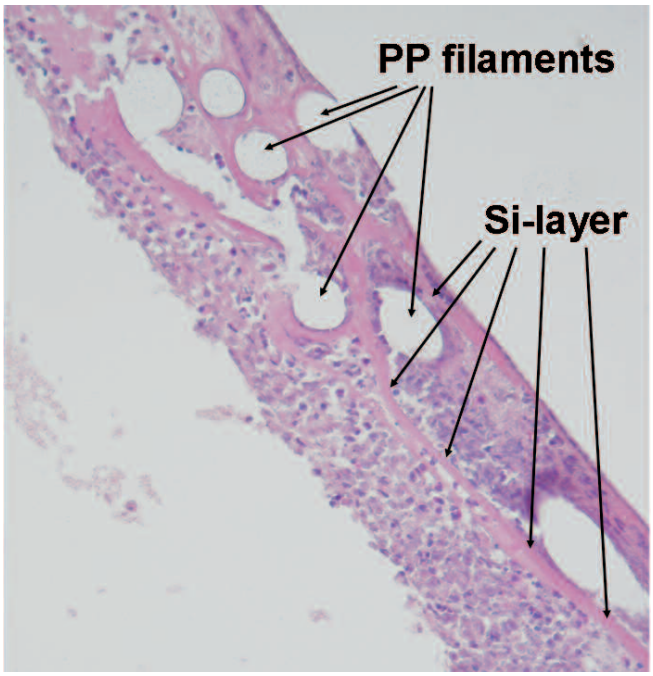


**Fig. 5.** HE staining, Lymphocytosis surrounding the filaments of LSPP mesh. The space of the mesh fibres, and the silicone layer is arrowed. x 20

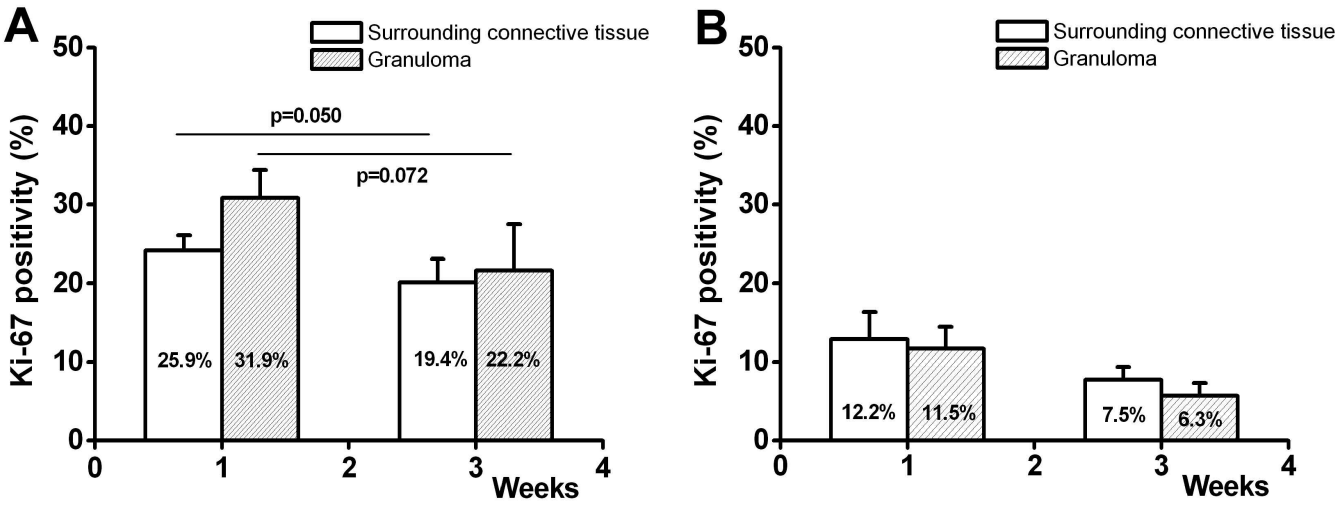


**Fig. 6. A.** Ki-67 positivity in LSPP containing tissues. **B.** Ki-67 positivity in MSPP containing tissues.

## Results

### *Adhesion formation*

All animals survived the operation, only 1 animal died before the planned termination (LSPP group; Diagnosis: Sepsis) for the rest no complication was seen during the follow-up period.

In the LSPP Group, 1 week after surgery the average rate of the affected mesh surface with adhesions was 30,5%. In half of the cases the visceral surface of the mesh was intact (Fig. 4). There were 2 meshes with large and small bowel loops adhering to the mesh and in the remaining 3 cases peritoneal and colon adhesions were detected on the silicone covering.

In the MSPP group, 1 week after surgery the average

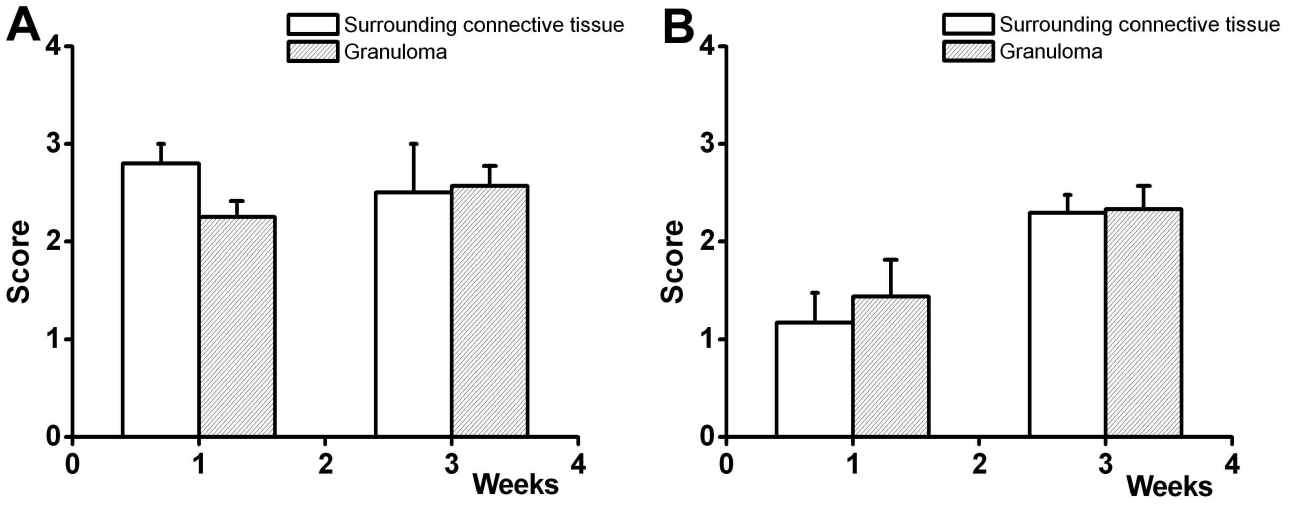


**Fig. 7. A.** VEGF positivity in the LSPP group. **B.** VEGF positivity in the MSPP group.

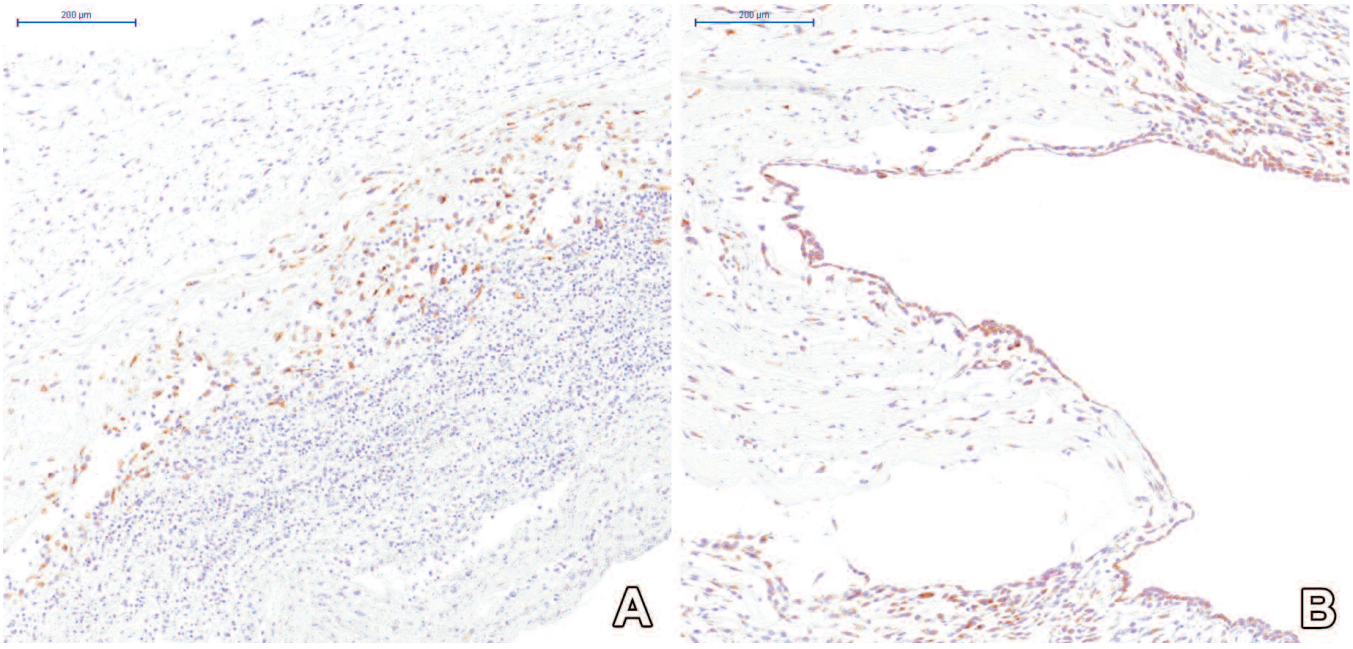


**Fig. 8. A.** CK positive cells in the LSPP group after 3 weeks. **B.** CK positive cells on the serosal surface of the MSPP containing section after 3 weeks . x 10

rate of the mesh surface was 37%. There were 3 cases with intact intraperitoneal surface found (Fig. 4-MSPP/A). In 2/10 cases the total mesh surface was covered with large intestine loops. In 2/10 cases only the cranial edge of the mesh was affected with peritoneal adhesions. (Fig. 4-MSPP/B)

In the LSPP Group 3 weeks postoperative the mean of the adhesion covered mesh surface was 22,2%. This decrease is not statistically significant (p=0.6). There were 7/10 intact meshes detected on the termination but in the remaining two cases the mesh was not visible because of the strongly adhered colon conglomerate, and in 1 case the urinary bladder was adhered to the caudal edge of the mesh.

In the MSPP Group 3 weeks after surgery the mean of the adhesion covered surface was 50.5%. There were 2 intact out of the 10 meshes, with vascularized newly formed good visible neoperitoneum on the intraperitoneal surface. In four cases intestinal, and in three cases out of 10 only peritoneal adhesions were detected on the intraperitoneal side of the silicone covered polypropylene mesh.

### *Complications*

In the LSPP group the seroma formation (5-24 ml) detected after 7 days was expected, but the infectious complications 3 weeks after implantation were surprising, namely 2 abscesses, 3 sc. haematomas, 3 fistula. In the MSPP group seroma-formation (5/20) and sc. haematoma (2/20) were observed.

### *Morphological studies*

HE staining was used to quantify the foreign body generated inflammatory reaction. The polymorphonuclear giant cells and lymphocytes were present in all slides. The conventional HE stained slides showed foreign body induced sterile inflammation with a decreasing tendency in the MSPP group, while in the

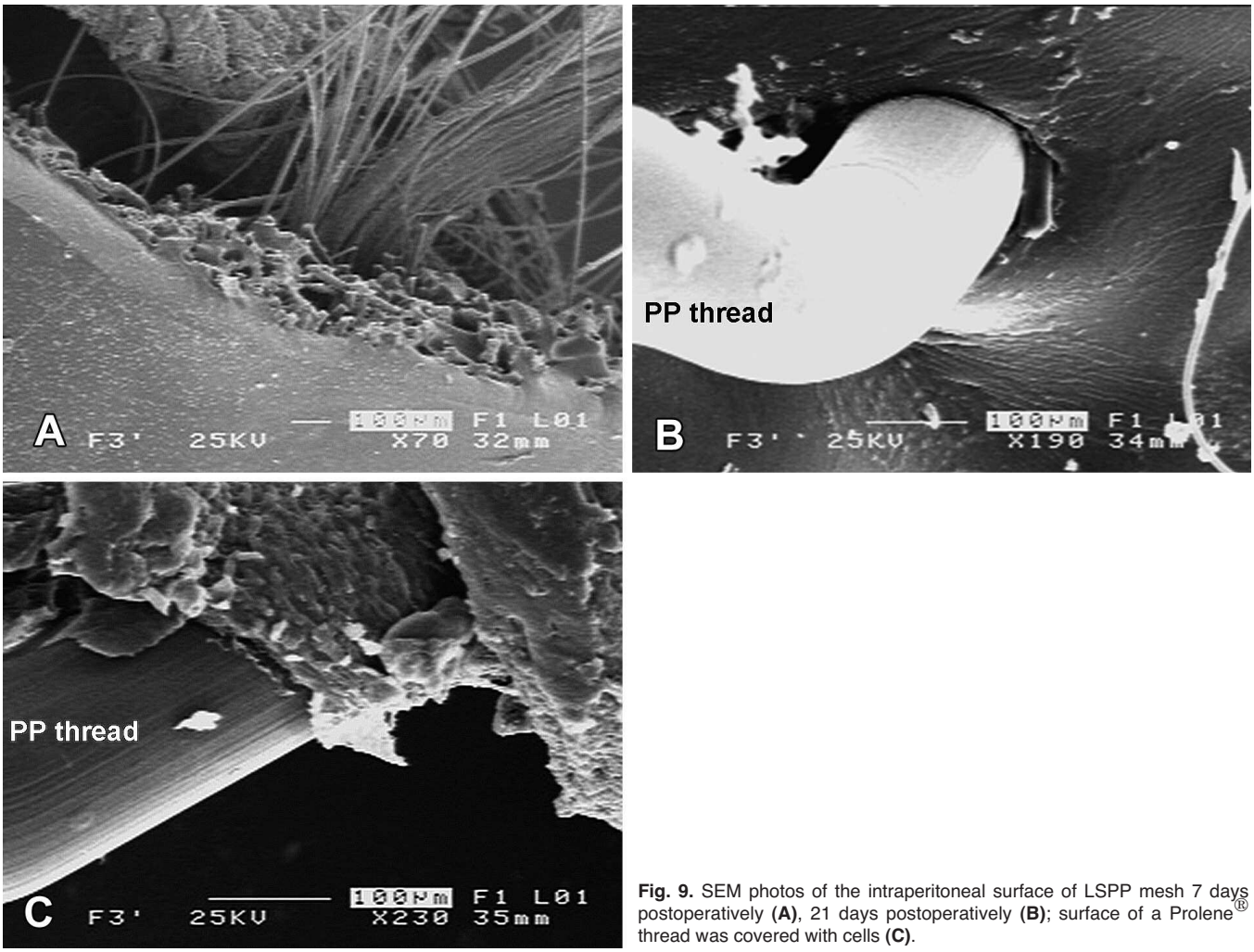


**Fig. 9.** SEM photos of the intraperitoneal surface of LSPP mesh 7 days postoperatively **(A)**, 21 days postoperatively **(B)**; surface of a Prolene® thread was covered with cells **(C)**.

LSPP group not only the connective tissue, but also the silicone layer was colonised by inflammatory cells and there was no decrease of inflammation detected after 3 weeks. (Fig. 5).

Ki-67 expression is a granular nuclear signal, which is easy to detect and count, representing mostly the inflammatory reactive cells.

The Ki-67 positive cells were separately counted in the granuloma (around the filaments of the mesh) and in the surrounding zone (further connective tissue). The proliferation index was significantly lower in all investigated groups after 3 weeks, than in 1 week old samples. The main difference between the meshes is the total number of the Ki-67 positive cells which was significant lower in the MSPP containing tissue (Fig. 6A,B).

With the VEGF immunostaining the vascularization of the newly formed peritoneal layer was demonstrated. The VEGF positivity showed no difference neither in relation with time, nor in affected areas in case LSPP mesh was implanted (Fig. 7A). While in the MSPP group the VEGF scores increased in 3 weeks (Fig. 7B).

MNF 116 broad spectrum cytokeratin (CK) specific mouse monoclonal antibody was used to visualize the mesothelial cells which were detected in each slide. The localisation and the get up of the cells after 1 week were the same in both groups. The triangle shaped, swollen positive cells were situated in the granulomatous zone around the foreign body. But in the LSPP group the slides stained with MNF 116 showed the same situation after 3 weeks (see Fig. 8A), which correlates well with the macroscopic findings, meaning no peritoneum was seen. In the MSPP group the recreation of mesothel after 3 weeks was well detectable in all cases. The MNF 116 positive cells were present in a monolayer on the serosal surface (Fig. 8B).

According to the macroscopic findings there was no tissue remodelling or neoperitoneum formation detected with Scanning electronmicroscopy in the LSPP mesh samples. The polypropylene thread used for fixation of the prostheses was better integrated than the silicone layer of the mesh (Fig. 9).

The electron microscopic evaluations showed an excellent ingrowth of the MSPP mesh. The thin cell layer over the filaments of mesh became a 3 dimensional tissue in 21 days (Fig. 10).

## Discussion

In the presence of a biomaterial, the wound repair process following surgery is conditioned by the structure of the prosthesis used (Pans and Pierard, 1992). The chemical composition of the surgical mesh does not seem to be the only that affects the repair process in the host tissue (Bellon et al., 2002). This comparative study was designed to evaluate the biological behaviour of 2 meshes with different textures but the same chemical composition. Expression of parameters representing wound healing and remodelling were examined, namely Ki-67, VEGF and CK.

Adhesions between the greater omentum and/or organs may be formed until neoperitonealization of the mesh is complete in about 1 week (Matthews et al., 2002). In the rat, intra-abdominal adhesions form within 24 hours after the operation and after 7 days no new adhesions were formed (van't Riet et al., 2003). Bellon et al. (2007) monitored the behaviour of the prosthetic material using sequential laparoscopy to follow the adhesion formation process during the 3, 7 and 14 days. He found that after the laparoscopy was performed at 7 days, the adhesions formed stabilized such that no progression was detected at 14$^{th}$ day of implant.

In this study the adhesion formation and the associated host reaction of the mesh were evaluated after

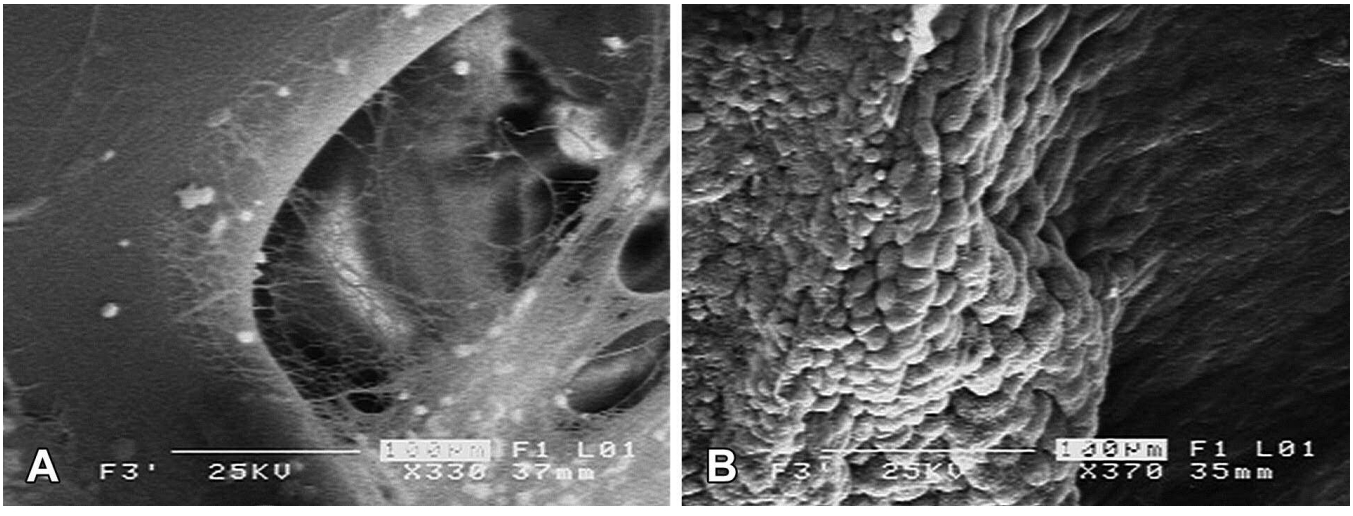


**Fig. 10.** Peritoneal surface of the MSPP mesh one **(A)** and three weeks **(B)** after implantation.

7 and 21 days. According to the above mentioned findings, our expectations of the first termination (7 days postoperatively) was to visualize the process of peritonealisation, while of the second termination (21 days postoperatively) to quantify and qualify the differences in adhesion formation due to the different tissue ingrowth.

The adhesion formation caused by the different meshes was similar 7 days after implantation ($p=0.9883$), while LSPP mesh caused less adhesions than MSPP ($p=0.0223$) after 3 week.

Host inflammatory reaction to the implanted material and haematoma may contribute to the formation of a seroma. Micropore meshes may have a higher tendency to form seromas than macropore materials, because passive drainage of the fluid to the peritoneal cavity through the mesh is diminished, but no study confirms this theory (Eriksen et al., 2007). When ultrasound examination is used to detect seromas, Susmallian et al. (2001) showed that all patients undergoing laparoscopis ventral hernia repair with ePTFE mesh developed a seroma in the first postoperative week.

The incidence of mesh infection varies between 6 and 9% after open ventral hernia repair (Bauer et al., 1999). The ePTFE mesh had a significantly higher infection rate than Marlex® mesh in a controlled retrospective study (n=37) published by Diaz et al. in 2004.

As van't Riet et al. (2003) reports the Parietex® composite mesh was more easily infected than the other meshes and showed a stronger inflammatory response. A stronger inflammatory reaction with an increased incidence of infection and formation of enterocutaneous fistulas (16%) with the use of polyester mesh was also found in a clinical study by Leber et al. (1998) This was in accordance to our results using the LSPP composite mesh. The incidence of fitulas was 30%.

Ki-67 is a widely used antibody to detect proliferating cells. Both in LSPP and MSPP meshes the granuloma zone showed a lot more proliferation activity than the surrounding zone and also the decreasing tendency of Ki-67 positivity in time was observed.

The main difference between the investigated meshes was the total number of Ki-67 positive cells, which represent the inflammatory reaction. A high number of positive cells were counted around the LSPP fibres and significantly lower positivity was detected in MSPP mesh containing tissue. That means the inflammatory reaction caused was lower using macroporous mesh.

In patients with abdominal hernias treated with primary or mesh repair, increased level of VEGF was detected in the early proliferative phase of wound healing in both serum and wound fluid (Karayiannakis et al., 2003). An important step in the incorporation of the mesh into the abdominal wall is the neoperitoneum formation and angiogenesis after the sterile inflammatory reaction calms down. The detection of newly formed capillaries and small vessels on the visceral surface of the mesh were not rare. Therefore, the VEGF antibody was used to follow the angiogenesis in this study.

The smooth silicone covering on the visceral surface of the LSPP mesh did not help neoperitoneum formation moreover, there was no increase in VEGF positivity with time. It represents well our macroscopic observations, that his mesh could not ingrown into the abdominal wall, and has been encapsulated in most of the cases. The MSPP mesh behaved as expected; meaning that neoperitonization was finished during the 3 weeks, the neoformed vessels were well visible and there was a significant increase in VEGF positivity following 3 weeks.

The immunhistochemistry to detect different fibroblast associated factors is well established. In our study the MNF-116 mouse monoclonal antibody was used to detect the mesothelial cells. In human practice this is a well known and widely used cytokeratin marker to detect the micrometastses of different carcinomas (Smeet et al., 2003; Biedrzycki et al., 2006).

The tissues removed 7 days postoperatively from both groups showed the same histological view. In CK stained slides the triangle shaped, swollen, positive cells were situated in the granulomatous zone around the foreign body granuloma in the deeper level. While after 3 weeks, in the case of MSPP mesh these positive cells were found mostly on the serosal surface of the tissue samples, creating a well organised monolayer covering the prosthetic. This was not seen in case of the LSPP mesh which is in accordance to the macroscopic observations.

Adhesion formation is a dynamic process influenced not only by the chemical properties of a prosthetic mesh but also its mechanical properties. As Schreinemacher et al. (2009) reports the preferential site of adhesion formation is at the cut edges of the mesh and the anchoring polypropylene sutures regardless of mesh types. In the case of coated meshes uncoated parts of the mesh presumably become exposed.

The results are in good accordance with the current literature reports that experimentally produced serosal defects lead to a partially defective fibrinolytic system, which increases adhesions to graft. It was noted that in the same setting omentum adheres to the mesh, thus preventing the intestine from adhering. Omentum reduces intraabdominal adhesions not only by interposing between abdominal viscera and mesh and creating a mechanical barrier, but also by producing fibrinolytic factors by its mesenchymal cells. Mesothelial cells harvested from rat greater omentum have been shown to reduce the adhesions resulting from peritoneal lesions by 60% (Karabulut et al., 2006).

In our experiment the laminar structure of silicone over the polypropylene mesh could not incorporate, there were a lot of infectious complications, and the only advantage was the lower area of adhesions according to the antiadhesive feature of it.

But if the pore-size of a polypropylene mesh is kept, and the adhesion formation is dependent on the filament coating, adhesions can be decreased as well, besides the excellent ingrowth into the abdominal wall which is the final solution for the abdominal wall hernias. This might be different in a laparoscopic model with just small wounds and less trauma, but further experiments are required.

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