Original Article

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An eligible biological allograft patch in tension-free herniorrhaphy of swine

Meihai Deng[1], Yuesi Zhong[1,*], Jian Yan[1], Kunpeng Hu[1], Zhicheng Yao[1], Cheng Chen[1], Guofeng Xu[2]

[1] *Department of General Surgery, Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China;*
[2] *Grandhope Biotech Co., Ltd., Guangzhou, China.*

Summary **Current patches made from macromolecular compounds or composix for tension-free herniorrhaphy are still unsatisfactory in biocompatibility. The ideal patch should be a biological patch with good biocompatibility. Herein allograft patches modified by tissue engineering were used in tension-free herniorrhaphy of swines. Tough membrane tissues from swine were modified with patented tissue engineering techniques to develop allograft patches for tension-free herniorrhaphy. Histological, and physical tests of the allograft patch were performed subsequently, which revealed that the allograft patch was sufficient and satisfactory for tension-free herniorrhaphy. The allograft patches were next used in tension-free herniorrhaphy of abdominal external hernia models of swines and compared to polypropylene patches. Serous $CD4^+$, $CD8^+$ T cells, interleukin-1β (IL-1β), and tumor necrosis factor α (TNF-α) were determined preoperatively and postoperatively. Local pathological changes were recorded postoperatively in swines. *In vivo* application of the allograft patches revealed that there were no significant serous cellular immune responses in swines, and inflammation induced by allograft patches was significantly lower compared to polypropylene patches, the allograft patches gradually degenerated and new collagen fibers appeared. Abdominal external hernias were cured with allograft patches and without relapse. The modified allograft patch with satisfactory biocompatibility was eligible and sufficient in tension-free herniorrhaphy of swine. Clinical trials should be performed for further evaluation of the allograft patch.**

Keywords: Biological allograft patch, tissue engineering modification, tension-free herniorrhaphy, swine

1. Introduction

External abdominal hernia is a frequently occurring disease that severely impairs quality of life and may sometimes be fatal. It is estimated that 1.5% of all people suffer from this disease. Worldwide, over 1 million external abdominal hernia surgeries are performed annually. The vast majority (90%) of external abdominal hernias are inguinal hernias and, in fact, 25% of males and 2% of females will develop an inguinal hernia during their lifetime, resulting in a high prevalence of external abdominal hernias (*1*). Roughly 3-20% of the patients undergoing open abdominal operations suffer from incisional hernias (*2*).

Surgical treatment of tensional herniorrhaphy revealed several shortcomings, and tension-free herniorrhaphy was first proposed by an American surgeon, Lichtenstein, in 1898 (*3*). Artificial patches were used for herniorrhaphy, which can minimize relapses and complications. There are two kinds of patches: artificial patches made from macromolecular compounds and biological patches (*4-6*). The most common macromolecular materials used for patches are polypropylene and polytetrafluoroethylene (*7-9*); however, there are several shortcomings of artificial

Deng MH and Zhong YS contributed equally to this work.

**Address correspondence to:*
Dr. Yuesi Zhong, Department of General Surgery, Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou 510630, China.
E-mail: zhongyuesi@gmail.com

macromolecular patches, *e.g*. chronic and long-term pain, foreign body sensation, patch translocation to other organs, formation of fibrous capsules, intestinal obstruction and relapse (*10-12*).

Researches have been focused on the use of composix mesh (*13-15*) or natural biological materials based on animal tissues (*16,17*); however, these materials are relatively unstable, degrade easily, and have poor mechanical strength. Furthermore, animal tissues may induce immunological rejection, thus adversely affecting their application (*18*).

Herein tough membrane tissues from swine were modified with tissue engineering techniques to develop allograft patches in tension-free herniorrhaphy of swines.

2. Materials and Methods

2.1. *Generation of the biological allograft patch*

Tough membrane materials from swines (Animal experiment center of Grandhope Biotech Co., Ltd. Guangzhou, China) were processed by a series of patented tissue engineering techniques (Patent Number: US 6, 101, 555 and US 6, 231, 614B1). Animal use was approved by the Animal Ethics Committee of Guandong province. These techniques included fixation of animal tissues, removal of antigenic epitopes, induction of tissue growth, modification of proteins and adjustment of degradation for the biological materials. Pericardium from fresh swines were collected, pretreated and fixed with an epoxide crosslinker, foreign antigens were removed and proteins were modified. After optimization of the physical strength, cutting, packaging and sterilization processes, the patch was developed.

2.2. *Morphological observation, and determination of physical parameters of the biological allograft patch*

Hematoxylin and Eosin (HE; IHC World, Woodstock, MD, USA) staining were performed on the biological allograft patch according to the manufacturer's instructions, and subsequently observed under a light microscope (Olympus, Tokyo, Japan). The biological allograft patch was also prepared for observation under an H-600 transmission electron microscope (Hitachi, Tokyo, Japan) for ultra microstructure.

Tensile strength and stretch rate of the biological allograft patch was determined with a micro-control electronic tensile testing machine (JPL, Jiangshu, China), and the sample was prepared and tested according to the manufacturer's instructions. Values were presented as N/cm and %.

2.3. *Tension-free herniorrhaphy to external abdominal hernia models of swines with allograft patches*

18 female swines (weight: 20-25 kg) were obtained from the animal experiment center of Grandhope Biotech Co., Ltd., Guangzhou, China. Animal use was approved by the Animal Ethics Committee of Guandong province. All swines were anesthetized 30 min before operations with ketamine hydrochloride injection (Shanghai No.1 Biochemical & Pharmaceutical Co., Ltd., Shanghai, China) by intramuscular injection (0.28 mL/kg). A 10 cm incision in the upper abdomen was made vertically through the linea alba to the parietal peritoneum in order to produce an external abdominal hernia.

All 18 female swines presenting with successful external abdominal hernias were equally and randomly assigned to 2 groups for tension-free herniorrhaphy 2 weeks after the first operation for the external abdominal hernia model, one group with allograft patches (n = 9), while the other group with polypropylene patches (C.R. Bard, Murray Hill, NJ, USA) (n = 9). The original incision was cut and the hernia sack was exposed. Tension-free herniorrhaphy was performed to repair the hernia. Swines were injected postoperatively and intramuscularly with penicillin at 50,000 IU/kg, twice a day (Baiyunshan Tianxin pharmaceutical Co., Ltd., Guangzhou, China) for 3 continuous days to prevent infection. 6 months after herniorrhaphy, 2 swines from each group were sacrificed for observation of the implanted patches, the other 14 swines were observed for 12 months after herniorrhaphy. All the implanted patches and surrounding tissues were observed under a light microscope (Olympus) and an H-600 transmission electron microscope (Hitachi).

2.4. *Serous $CD4^+$, $CD8^+$ T cells, interleukin-1β (IL-1β), and tumor necrosis factor α (TNF-α) of swines*

Serum samples were collected from all swines before herniorrhaphy, 1 week and 4 weeks after herniorrhaphy for determination of $CD4^+$, $CD8^+$ T cells, IL-1β, and TNF-α. Briefly, three-color flow cytometry was employed using an Enzymatic Amplification Staining Kit (Flow-Amp Systems, Tebu-bio, Le Perray en Yvelines, France) for proportions of $CD4^+$, and $CD8^+$ T cells. Specific anti-swine antibodies: anti-CD4-FITC, anti-CD8-FITC (Southern Biotechnology Associates Inc., Birmingham, UK) were used according to the manufacturer's instructions. An enzyme-linked immunosorbent assay was used to detect the concentration of IL-1β and TNF-α in the serum, rabbit monoclonal anti-IL-1β and anti-TNF-α (Becton Dickinson, Franklin Lakes, NJ, USA) were used as the primary antibodies.

2.5. *Statistics*

Data are presented as the means ± S.D. Student's t-tests were used for statistical analyses. SPSS 11.5 for

windows was used. A value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. *Morphology and physical parameters of the biological allograft patch*

The biological allograft patches displayed a milky white color. One side of the patch was smooth while the other side had faint striated structures. Patches contained small, evenly distributed holes (Figure 1A). The maximum patch size was 21 × 16 cm with a thickness of 0.3-0.7 mm. The patches were fairly flexible and plastic, and were easily sutured and tailored.

HE staining showed that the patch was composed of regularly-aligned collagen, and displayed no evidence of cells or vessels (Figure 1B). Transmission electron microscopy revealed that the collagen was aligned regularly and inseparably. Cells and vessels were not seen (Figure 1C).

The physical parameter of tensile strength of the biological allograft patch was 90-160 N/cm (median 125 N/cm), and the stretch rate of the biological patch was 62-82% (median 71%).

3.2. *External abdominal hernia models and tension-free herniorrhaphy with allograft patches*

All swines survived the operation of the external abdominal hernia model. In the operation, muscle laying on both sides of the linea alba was separated and the enclosed muscle fiber was transected, leading to the formation of an 8 × 6 cm defect area (Figure 1D), 2 days later, the incisional sites began to protrude, and 7 days after operation, a classical external abdominal hernia had formed (Figures 1E and F). The size of the hernia was 12 × 10 cm, projecting 4 cm over the skin when the swine was in the court position.

There were no infections or impaired wound healing for both groups that underwent tension-free herniorrhaphy with allograft or polypropylene patches. In tension-free herniorrhaphy with allograft patches, the allograft patch was placed onto the defect area, and overlaps between the patch and hernia had to be larger than 1 cm (Figures 1G and H). All external abdominal

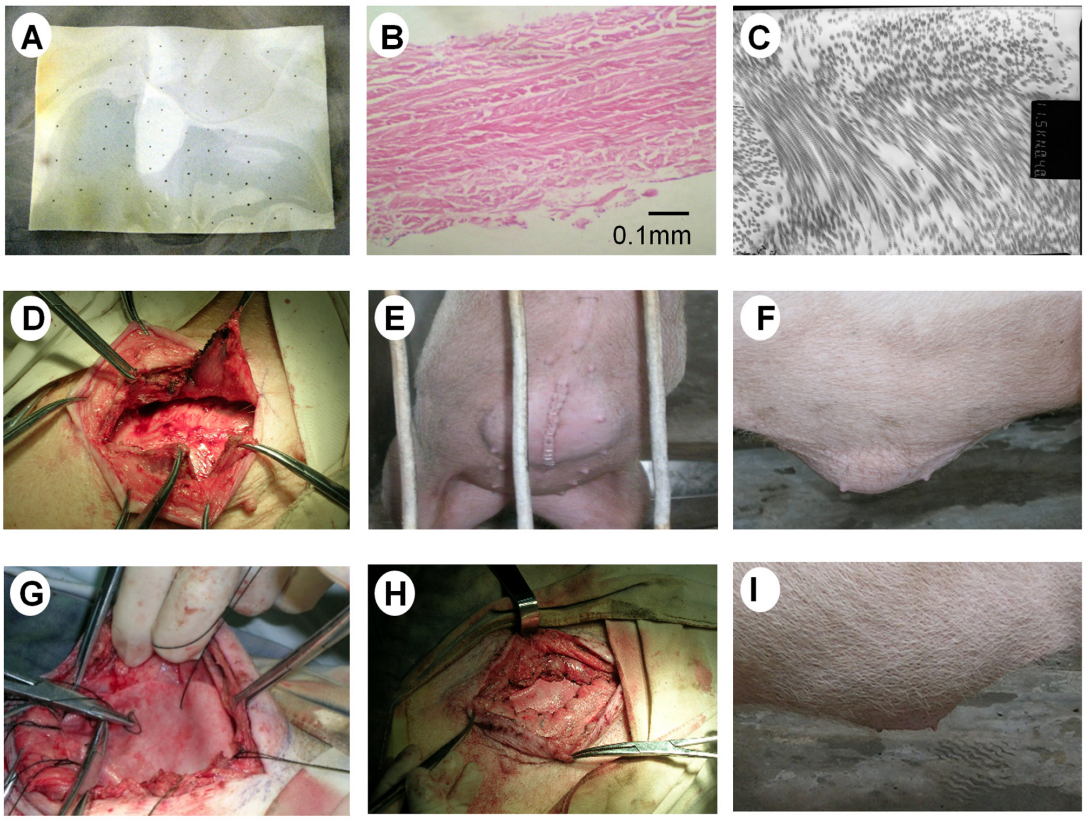

Figure 1. Histological observation of the biological allograft patch and its subsequent application in tension-free herniorrhaphy to external abdominal hernia models of swines. The biological allograft patch that has small, evenly-distributed holes **(A)**; Regularly-aligned collagen was observed and cells were not observed in the patch according to HE staining **(B)**; Collagen was aligned regularly and inseparably, cells and vessels were not observed according to transmission electron microscopy **(C)**; In operation of model of external abdominal hernia, muscle laying on both sides of the linea alba was separated and the enclosed muscle fiber was transected, leading to the formation of a 8 × 6 cm defect area **(D)**; A classical external abdominal hernia had formed 7 days after the operation of model **(E, F)**; In tension-free herniorrhaphy, process of suturing the patch with the swine tissues **(G)**; Observations after the allograft patch was implanted onto the defect area, the overlaps between the patch and hernia were larger than 1 cm **(H)**; The external abdominal hernia was cured without relapse 12 months after herniorrhaphy **(I)**.

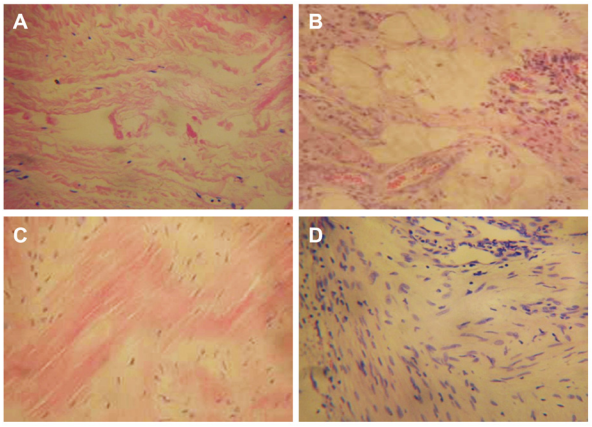

Figure 2. Histological observation under light microscopy of the allograft and polypropylene patches 6 and 12 months post-herniorrhaphy. Degenerated and broken collagen fibers appeared, and many fibroblasts and fibrocytes were observed in allograft patches 6 months after herniorrhaphy (×200) **(A)**; Megakaryocytes and fibrocytes among polypropylene patches were observed and collagen fibers appeared irregularly 6 months after herniorrhaphy (×200) **(B)**; New regular collagen fibers were observed among the allograft patch 12 months after herniorrhaphy (×200) **(C)**; Megakaryocytes and irregular new collagen fibers were observed among polypropylene patches 12 months after herniorrhaphy (×200) **(D)**.

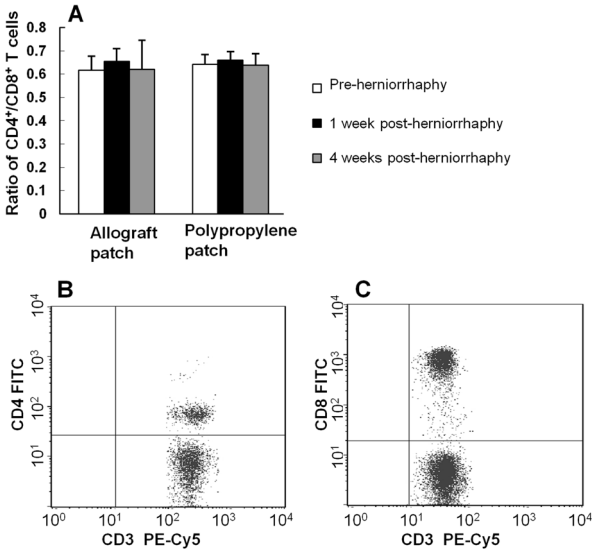

Figure 3. Serous ratios of $CD4^+/CD8^+$ T cells of swines in both groups. There were no significant differences of serous ratios of $CD4^+/CD8^+$ T cells between groups of allograft and polypropylene patches before herniorrhaphy, 1 week and 4 weeks after herniorrhaphy **(A)**; Proportions of serous $CD4^+$ and $CD8^+$ T cells in one swine 4 weeks after herniorrhaphy were 23.22% **(B)** and 34.18% **(C)**, respectively.

hernias of swines were cured without relapses within 12 months observation after herniorrhaphy (Figure 1I).

3.3. *Histological analysis of implanted allograft patches 6 months and 12 months after tension-free herniorrhaphy*

Six months after herniorrhaphy, degenerated and broken collagen fibers appeared, and many fibroblasts and fibrocytes were observed in allograft patches under light microscopy (Figure 2A). The allograft patches were surrounded by a large number of fibroblasts, eosinophils, lymphocytes and continuous wave-like collagens, which were confirmed with transmission electron microscopy. Light microscopy for polypropylene patches revealed that there were lots of megakaryocytes and fibrocytes among polypropylene patches, collagen fibers appeared irregularly (Figure 2B).

Twelve months after herniorrhaphy, there were new collagen fibers appearing and presenting regularly, and a few sporadic fibroblasts among the allograft patches (Figure 2C). Results of polypropylene patches revealed that there were lots of megakaryocytes among polypropylene patches and new collagen fibers appearing irregularly (Figure 2D).

3.4. *Determination of serous $CD4^+$, $CD8^+$ T cells, IL-1β, and TNF-α of swines*

The proportions of $CD4^+$ cells and ratios of $CD4^+/CD8^+$ T cells of swines between groups of allograft and polypropylene patches were not significantly different pre-herniorrhaphy, 1 week and 4 weeks post-herniorrhaphy (Figure 3). In the group of allograft patches, the proportions of $CD4^+$ cells and ratios of $CD4^+/CD8^+$ T cells of swines were not significantly different between pre-herniorrhaphy, 1 week and 4 weeks post-herniorrhaphy (Table 1). ELISA results revealed that serous IL-1β (Table 2) and TNF-α (Table 3) increased 1 week post-herniorrhaphy, and decreased 4 weeks post-herniorrhaphy but remained higher than that of pre-herniorrhaphy. Results of the IL-1β and TNF-α group of polypropylene patches were significantly higher than that of the group of allograft patches.

4. Discussion

Studies on scaffold materials are one of the most important research areas in tissue engineering. Not only can scaffold materials fix structural tissue damage, but they can also provide a three-dimensional vector with which functional cells can anchor, grow and proliferate. As the scaffold materials are degraded and absorbed, gradually new, regenerated tissue begins to replace the old and diseased tissue leading to functional improvement of the pathological tissue or organ (*19*). Materials for external abdominal hernia repair also belong to the category of scaffold material research areas (*20*).

Lately, research on biological patches has been focused on the use of animal tissue-based natural materials (*21*).

Classical methods for treating the animal tissue are based on using glutaraldehyde for fixation and

Table 1. Proportions (%) of $CD4^+$ T cells and ratios of $CD4^+/CD8^+$ T cells of swines in the group of allograft patches

Items	pre-herniorrhaphy	1 week post-herniorrhaphy	4 weeks post-herniorrhaphy
Proportions (%) of $CD4^+$ T cells	21.89 ± 2.24	23.11 ± 1.94	21.93 ± 2.24
Ratios of $CD4^+/CD8^+$ T cells	0.618 ± 0.059	0.656 ± 0.054	0.621 ± 0.124

$p > 0.05$

Table 2. Serous IL-1β of swines in both groups (pg/mL)

Items	pre-herniorrhaphy	1 week post-herniorrhaphy	4 weeks post-herniorrhaphy
Group of allograft patch	8.98 ± 5.79	202.31 ± 17.41*	38.60 ± 25.87**
Group of polypropylene patch	10.13 ± 1.83	321.70 ± 78.84*	70.36 ± 21.89**

* $p = 0.014$, ** $p = 0.028$

Table 3. Serous TNF-α of swines in both groups (pg/mL)

Items	pre-herniorrhaphy	1 week post-herniorrhaphy	4 weeks post-herniorrhaphy
Group of allograft patch	5.69 ± 2.72	54.33 ± 8.17*	10.76 ± 8.87**
Group of polypropylene patch	4.32 ± 2.76	94.67 ± 13.02*	12.99 ± 10.85**

* $p = 0.008$, ** $p = 0.039$

crosslinking (*22*); however, crosslinking using glutaraldehyde yields unstable acetalization and produces toxic glutaraldehyde around the tissues, making it very difficult for host tissue to fuse and grow within the implanted animal tissue. Furthermore, acetalization does not completely remove foreign antigens. This is one of the bottlenecks that prevented the rapid development and advancement of biological materials across the world.

A new technique (Patent Number: US 6, 101, 555 and US 6, 231, 614B1) was developed to eliminate the toxic glutaraldehyde and completely remove the foreign antigens. Using a highly reactive epoxide as a fixation and crosslinking reagent, this epoxide can form stable cross bonds with protein, which significantly improves stability and eliminates toxicity. Moreover, the technique can induce the growth of host tissues into the implanted tissues, leading to the fusion of self tissue with implanted materials, which was confirmed by current results, 6 months after tension-free herniorrhaphy, the former regularly-aligned collagen degenerated and was broken, and many fibroblasts and fibrocytes were observed in the implanted allograft patch. 12 months after tension-free herniorrhaphy, new collagen fibers appeared and presented regularly, and there were no relapsed cases.

In addition, the technique involving modification of the protein molecules can also improve the physical mechanical parameters of the allograft patch. The tensile strength of the allograft patch was 90-160 N/cm, and the stretch rate was 62-82% according to the results. The maximum tensile strength placed on the abdominal wall in healthy adults ranges from 11 N/cm to 27 N/cm (*23*), and the bursting forces of the standard polypropylene patch have been measured at 40 to 100 N/cm (*24*). At 16 N/cm, the abdominal wall distends about 25%; however, polypropylene patches displayed a value of only 4-16% strain (*25*), which was possibly responsible for postoperative complaints of discomfort. The tensile strength of the biological allograft patch was almost 4 times maximum tensile strength of the abdominal wall in healthy adults, and was larger than that of the polypropylene patch, the stretch rate was also larger than that of the polypropylene patch and the abdominal wall.

Our current results revealed that all 9 swines implanted with allograft patches survived and were cured after tension-free herniorrhaphy without local infection. Serous IL-1β and TNF-α were both increased after herniorrhaphy, results of the IL-1β and TNF-α group of polypropylene patches were significantly higher than that of the group of allograft patches. TNF-α is a cytokine involved in inflammation, and IL-1β is a member of the interleukin 1 cytokine family, which is an important mediator of the inflammatory response. Thus allograft patches produced significantly lower inflammation to the host when compared to polypropylene patches.

$CD4^+$ T cells are also known as T helper cells, and $CD8^+$ T cells are also known as cytotoxic T cells, both $CD4^+$ and $CD8^+$ T cells are important in cellular immune responses and are also implicated in transplant rejections (*26*). The proportions of serous $CD4^+$ T cells and ratios of $CD4^+$/ $CD8^+$ T cells increased 1 week post-herniorrhaphy with allograft patches, which was not significant. The results of 4 weeks after herniorrhaphy were not significantly different when compared to that of pre-herniorrhaphy and 1 week post-herniorrhaphy. The allograft patches revealed satisfactory biocompatibility according to the results.

Ideal patches for tension-free herniorrhaphy are biological patches with similar components to

host tissues. They should also meet the following requirements (*27-29*): (1) stable compatibility without inflammation; (2) sufficient physical strength; (3) scaffold provision for self regeneration; (4) non-toxic and non-carcinogenic; (5) easy to produce, sterilize, preserve and tailor. Our results strongly indicate that the allograft patches used in the present study are promising for overcoming complications induced by macromolecular or composix patches, *e.g*. chronic, long-term pain, foreign body sensations, conglutination and so on and are a candidate for an ideal patch for tension-free herniorrhaphy.

5. Conclusion

The tissue engineering modified allograft patch with satisfactory biocompatibility is eligible and sufficient in tension-free herniorrhaphy of swine, and is a candidate for ideal patches for tension-free herniorrhaphy. Clinical trials should be performed for further evaluation of the allograft patch.

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