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Is fetal tissue the only factor responsible for the properties of fetal wound healing?

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Abstract  Fetal skin wounds heal without inflammation, collagen deposition or wound contraction. The mechanism of this process is unknown, but may be unique to fetal cells, the fetal environment, or an combination of both. In order to determine whether fetal cells are the only factor responsible for scarless wound healing, an experimental study was performed on ten cats who were in the last trimester of their pregnancy. Skin grafts were transferred from mother to fetus and fetus to mother. The fetal skin grafted to the mother was biopsyed between the eighth and tenth postoperative days and was evaluated histopathologically on days 18–20. Biopsy revealed scar formation in both the fetal grafts in the adult and maternal grafts in the fetus. We can conclude that scarless wound healing in the fetus is not solely due to fetal cells.

Key words  Fetal wound healing · Fetal graft healing · Maternal graft healing

Introduction

The healing of incised fetal wounds without inflammation, collagen deposition and wound contracture has attracted the interest of many investigators. Although interest in this subject dates back to the 1950’s aside from a few investigations performed in the 1970’s, it was only in the 1980’s that many unknown components of fetal wound healing were uncovered [1, 9, 13, 15]. The latter studies have explored the properties of fetal wound healing by intrauterine interventions and sought ways to apply these to the adult wound [2, 6, 10, 14].

The properties of fetal wound healing have been attributed to fetal cells and/or fetal environment, especially amnion. To determine the involvement of each factor, Ledbetter et al. [5] covered an excised fetal wound with silicone coating to prevent contracture with amniotic fluid and found that while the uncovered wound healed without contracture, the healing of the wound amnion contact was the opposite. Longaker et al. [11] performed on skin grafting from mother to fetus, after healing maternal grafts and fetal skin were incised and sutured the resulting wounds on maternal graft and fetal skin. Histopathological examination on the 14th day showed that both wounds healed in their characteristic ways. This shows that the healing properties of adult tissue is not altered by the presence of amniotic fluid.

In this experimental study, an attempt was made to determine the effect of fetal tissue cells on fetal type wound healing by histopathological analysis of a fetal graft on an adult.

Material and methods

Cats were chosen for this experimental study because they are resistant to infection and environmental factors.

This study group consisted on ten cats in the trimester of pregnancy. The cats were anesthetized using 2% xylazine, 0,1 mg/kg IM (Rompun: 23,32, mg), and ketamine hydrochloride 20 mg/kg (50 mg/kg). After induction of anesthesia, ritodrine 50 mg/kg (Pre- par) 0,5 mL IM was injected for tocolysis.

Laparotomy was carried out and after hysterotomy, the back of the fetus was delivered through the wound and 1x1 cm skin grafts were taken. The wound was then closed with abdominal skin grafts taken from the mother using #4-0 atrumatic silk (Fig. 1). After saline injection into the uterus, hysterotomy and laparotomy were closed in the standard fashion (Fig. 2). The skin grafts of the fetus were applied to the donor sites of maternal skin grafts on the right side of the laparotomy incision.

On the tenth postoperative day, under local anesthesia, on the skin of the mother two incisions were made on the fetal grafts and one of them was sutured while the other one was left unsutured (Fig. 3). Between postoperative days 8–10, after the second intervention, the grafts were removed under local anesthesia and examined histopathologically.
Results

Although tocolytics were injected prior to laparotomy for prevention of abortion, there was one early intrauterine fetal death causing septicemia in the mother. This animal was re-explored and one dead and two living fetuses were delivered. However, the mother died one day post-laparotomy. This animal and the live fetuses were excluded from the study. The remaining nine animals gave birth 7–12 days after laparotomy, except one animal which underwent laparotomy on the eighth postoperative day because of its poor general condition; one dead and one living fetus were delivered. The other eight fetuses were investigated histopathologically. Two of the fetuses were lost due to maternal cannibalism.

The fetal grafts applied to the adults were seen to heal with scar formation. Regardless of the incisions or excisions, the fetal grafts applied to the adults have also healed with scar formation. Histopathological examination revealed the following findings:

- Histopathologic studies on eight fetal grafts in adults have shown histiocyte proliferation extending from the epidermis to the reticular dermis, mostly condensing around the skin adnexae in the incised and sutured grafts. Connective tissue and fibroblast activation were also noted in these areas (Fig. 4).
- Examination on the eighth day revealed granulation tissue and fibroblastic activity.
- Examination on the tenth day revealed lymphohistiocytic infiltration and an increase in the connective tissue together with the collagen production, specific for scar formation.
• There was no difference between sutured and nonsutured wounds. Both have healed with granulation tissue and scar formation.
• The histopathological studies on eight maternal grafts in the fetus revealed that minimal fibrohistiocytic proliferation and slight proliferation in capillary vessels.
• Maternal grafts on the fetus, applied in utero, were found to lead to less scar tissue than the fetal grafts (Fig. 5).

Discussion

Fetal tissue are immunologically deficient compared to adult tissues. This may be due to lack of antigenic experience of the fetal immune system, insufficient chemotaxic function despite a normal phagocytic function and fetal neutropenia [4]. This is the reason why fetal grafts do not undergo early rejection in the adult. In this era of organ transplantation, minimal graft versus host reaction of fetal tissues has emerged as an alternative [12]. We did not expect rejection of the fetal allograft on the mother in the first ten days. Long-term results cannot be commented on because the incised grafts were removed on the 18th day for histopathological examination. Histopathological examination 18–20 days after grafting revealed that there were no rejection and the grafts had healed by the normal wound healing process.

While searching for the properties of fetal wound healing, Longaker applied maternal grafts to the fetus as well as fetal skin thus causing them to heal with fetal blood supply and in contact with amniotic fluid [11]. The outcome of this study revealed that the grafts taken from the adult healed with fibrosis and granulation tissue. The conclusion was the fetal environment is not the sole responsible factor for properties of fetal wound healing.

In our study, the grafts taken from the fetuses healed with scar formation and inflammation. This is in contrast to the findings of Haynes et al. who proposed that fetal cells lack contractile elements [3]. There was no histopathological difference between sutured and nonsutured wounds on the grafts except that nonsutured wounds have healed with wound contracture. These findings point out that the healing of fetal grafts applied to adults is adult type healing.

On the other hand, the maternal grafts were observed to heal with minimal scar formation. However, this minimal fibrohistiocytic proliferation may be due to insufficient fetal host reaction.

Our results indicate that fetal type wound healing is not attributable only to the pre-existing properties of fetal cells. The amniotic fluid, the low oxygen pressure, etc., may also have a role in such wound healing. We conclude this observation is of interest in the sense that these findings can be applied to adults.

References