

Decorin Inhibits Dermal Mesenchymal Cell Migration and Induces Scar Formation

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Background: Variations in skin healing capacities are observed during different murine embryonic developmental stages. Through embryonic day 16 (E16), embryos are able to regenerate dermal architecture following flank skin wounding; however, after E17, wounds heal incompletely, inducing scar formation. The regenerative ability of the E16 fetal dermis depends on the migration of dermal mesenchymal cells. Decorin is a small molecule known to affect tissue tensile strength, cell phenotype, and tissue repair, including skin wound healing. In the current study, we evaluated the expression and roles of decorin in wound healing. **Methods:** Surgical injury was induced at E16 and E17 in ICR mouse embryos. Decorin expression was evaluated in tissue samples from these embryos using immunohistochemistry and reverse transcription quantitative polymerase chain reaction. Cell migration assays were used to evaluate wound healing capability of separated dermal and fascial tissues.

Results: Our results showed that decorin exhibited distinct expression patterns during wound healing at E16 versus E17. Additionally, decorin expression altered cell migration in vitro. Dermal and fascial mesenchymal cells were found to exhibit distinct migration patterns concomitant with altered decorin expression. Specifically, decorin inhibited migration and favored scar formation.

Conclusion: Decorin expression may contribute to scar formation in the late stage of mouse embryos by inhibiting the migration of dermal mesenchymal cells. (*Plast Reconstr Surg Glob Open* 2022;10:e4245; doi: 10.1097/GOX.0000000000004245; Published online 11 April 2022.)

INTRODUCTION

Adult mammals cannot completely regenerate injured tissue. Although injured organs can be healed, this typically involves some degree of scarring, except in a limited number of organs (such as the liver).¹ However, wounded mammalian skin is capable of complete regeneration at certain embryonic developmental stages.² In the dermis of Jcl:ICR mice, up to embryonic day 16 (E16), the skin architecture is completely restored after injury.³ After E17, however, scar formation occurs.³ Epidermal regeneration during wound healing is dependent on deep muscle fascia. Cutaneous mesenchymal cells of an E16 wound migrate between the epidermis and fascia after re-epithelialization

is complete, thereby eventually regenerating the complete dermal structure. In contrast, dermal mesenchymal cells do not migrate toward the site of injury during E17 wound healing, and fascial mesenchymal cells instead elaborate scar tissue.⁴ However, the mechanism behind switching off dermal mesenchymal cell migration to the site of injury and switching on fascial mesenchymal-cell-mediated scarring during later embryonic stage wound healing remains unclear.

Decorin (a small, leucine-rich proteoglycan) is expressed in a variety of connective tissues, such as the skin, cartilage, and bone. In conjunction with collagen fibrils, decorin is involved in the assembly and structural organization of extracellular matrix components.⁵ Moreover, decorin also inhibits the migration of certain tumor cells in vitro.⁶ Through these functions, decorin is thought to affect wound healing and inhibit tumor progression.⁷⁻⁹ Decorin expression has been reported to change during embryonic wound healing¹⁰; however, the mechanistic relationships between these changes and cell migration into and out of the site of injury have not yet been elucidated.

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In the current study, we evaluated the correlation between decorin expression at the site of injury and migration of dermal mesenchymal cells into the wound during the later stages of E16 wound healing. In particular, we focused on wounds within 48 hours of injury because wound healing in mouse fetuses progresses rapidly.⁴ In addition, we evaluated changes in migration response to decorin expression in embryonic dermal cells and fascial mesenchymal cells in vitro. Our findings provided insights into the contribution of decorin expression to regeneration of dermal structure.

METHODS

Ethical Considerations

The study protocol was reviewed and approved by the Institutional Animal Care and Use Committee of Keio University School of Medicine [approval number: 13072-(2)]. All experiments were performed in accordance with Keio University Institutional Guidelines on Animal Experimentation.

Embryonic Wounding and Skin Harvesting

Eight-week-old ICR mice were obtained from Sankyo Laboratories, Japan. Embryos were designated as E0 when a mucus plug was observed in the maternal vagina. Surgical injuries were introduced at E16 and E17. Briefly, anesthesia was induced in pregnant dams with 4% isoflurane (FUJIFILM Wako Pure Chemical Co., Osaka, Japan), which was maintained at 2% during surgery. The surgical site was sterilized using 70% ethanol, the myometrium and amniotic membrane were opened laparotomically, and a 2-mm-long full-thickness incision was made on each flank of the embryo using sterilized microsurgical scissors (Medical U&A, Inc. Osaka, Japan; n = 12 fetuses per time point). The myometrium was closed with purse string sutures using 9-0 nylon to separate the embryo from the maternal pelvic fluid, and the maternal abdominal wall was sutured similarly using 4-0 nylon (Medical U&A, Inc.). At multiple time points postinjury, animals were killed by cervical dislocation following anesthesia via inhalation of 4% isoflurane.

Wounded embryonic skin was harvested 24 and 48 hours postinjury. Skin from the uninjured side was used as control tissue and for assessment of decorin expression during normal skin development. Tissue specimens were fixed by immersion in 4% paraformaldehyde, which was then replaced with 30% sucrose solution prior to snap-freezing tissue in Tissue-Tek O.C.T. compound (Sakura Finetek Japan, Tokyo, Japan). Finally, specimens were transferred to -70°C for storage until sectioning. In parallel, additional tissue specimens were fixed, embedded in paraffin, and maintained at room temperature (15°C – 25°C) until sectioning.

Immunohistochemistry

Frozen specimens were sliced into 7- μm -thick sections, mounted on glass slides, and then fixed in dry acetone for 10 minutes at room temperature. After heat-induced antigen retrieval, slides were incubated with 2% goat serum in phosphate-buffered saline (PBS) for 30 minutes at room

Takeaways

Question: What is the extent and role of decorin expression in wound healing and scar formation?

Findings: In our unique mouse fetal wound healing model, decorin expression was involved in scar formation; in vitro cell migration observations showed that decorin inhibited the migration of cells involved in skin regeneration.

Meaning: Decorin inhibited cell migration and favored scar formation.

temperature in order to block nonspecific binding sites. Slides were then incubated with a 1:100 dilution (in PBS) of the primary antibody (rabbit antidecorin antibody; LSBio, Seattle, Wash.) overnight at 4°C . After washing three times with PBS, slides were incubated with a 1:200 dilution (in PBS) of Alexa Fluor 488-conjugated goat antirabbit antibody (Thermo Fisher Scientific, Waltham, Mass.) for 1 hour at room temperature. After washing three times with PBS, nuclear counterstaining was performed using ProLong Gold antifade mountant containing 4',6-diamidino-2-phenylindole (Thermo Fisher Scientific).

Paraffin-embedded specimens were similarly sliced into 7- μm -thick sections and mounted on glass slides. After drying overnight at room temperature to allow the samples to adhere to the slides, the paraffin was dissolved in a 65°C slide heater (ThermoBrite; Leica Biosystems, Nussloch, Germany) for 30 minutes immediately prior to use. Slides were then deparaffinized in two changes of xylene (5 min each) at room temperature. The slides were rehydrated by transferring to 100% ethanol for two changes (3 min each) and then transferred once through 95%, 70%, and 50% ethanol (3 min each) at room temperature. Antigen retrieval, blocking, and primary antibody incubation were performed as described above. After washing three times with PBS, slides were incubated with a 1:500 dilution (in PBS) of biotinylated goat antirabbit antibody (Vector Laboratories, Burlingame, Calif.) for 1 hour at room temperature. The signal was amplified via the avidin-biotinylated peroxidase complex method using a VECTASTAIN avidin-biotinylated peroxidase complex kit (Vector Laboratories), and color was developed using a 20 mg per dL 3,3'-diaminobenzidine solution (FUJIFILM Wako Pure Chemical Co.) for 1–3 minutes. Sections were then washed once for 5 minutes with running tap water prior to nuclear counterstaining using Gill's hematoxylin solution (Merck Millipore, Billerica, Mass.) for 6 seconds at room temperature. Finally, sections were washed for 5 minutes with running tap water, rinsed to dehydrate with four changes of ethanol (95%, 95%, 100%, and 100%; 5 min each), cleared with three changes of xylene, and sealed using Mount-Quick sealant (Takara Bio, Shiga, Japan). Slides were visualized using an all-in-one stereomicroscope (BZ-X800; KEYENCE, Osaka, Japan).

RNA Extraction and Reverse Transcription

Wounds were excised from injured skin under a stereomicroscope, cutting as close to wound margins as possible.

Total skin RNA was extracted from both injured and uninjured specimens using a single-phase solution of phenol and guanidine isothiocyanate (ISOGEN; Nippon Gene, Tokyo, Japan), according to the manufacturer's instructions. Total extracted RNA was mixed with random primers, reverse transcriptase, and a dNTP mixture (Takara Bio) and subjected to reverse transcription to produce cDNA.

Reverse Transcription Quantitative Polymerase Chain Reaction

Previously reported methods for reverse transcription quantitative polymerase chain reaction and transcript quantification were employed.¹⁰ Briefly, decorin transcript levels were quantified from the different samples (in triplicate) using TaqMan Gene Expression Master Mix (Thermo Fisher Scientific) in an Applied Biosystems 7500 Fast real-time PCR system (Thermo Fisher Scientific). As an endogenous normalization control, we used the house-keeping gene *ACTB*.

Boyden Chamber Migration and Scratch Assays

After microscopy-assisted wound excision in a manner identical to that described above, E17 skin and underlying fascial mesenchymal tissue were separated using a microsurgical device in conjunction with surgical microscopy (Leica Biosystems). Separated dermis and fascia were then explanted into separate plastic dishes for primary culture of local mesenchymal cells. After passages 5–7, cells were subjected to migration assays. Before each assay, cells were treated with mitomycin C (NAKARAI TESQUE, INC., Kyoto, Japan) to exclude proliferative effects (10 $\mu\text{g}/\text{mL}$ for 3 hours at 37°C). To prepare Boyden chambers (Sigma-Aldrich, St. Louis, Miss.), the underside of a 12- μm polycarbonate membrane was coated with 1.2 μg per mL fibronectin (Corning Inc., Corning, N.Y.) and 1.5 or 15 μg per mL decorin (Research and Diagnostic Systems Inc.,

Minneapolis, Minn.). Cells (1×10^4) were placed on the upper membrane surface and incubated for 2 hours at 37°C in 5% CO_2 with 95% relative humidity. The number of cells that had migrated through membrane pores was counted under a microscope. For scratch assays, cells were grown to confluence on plastic dishes, and a 500- μm scratch was made with a pipette tip. Cells were cultured in Dulbecco's modified Eagle's medium supplemented with 50 μg per mL decorin for up to 24 hours at 37°C in 5% CO_2 with 95% relative humidity. Cell migration from scraped edges was visualized under a microscope (BZ-X800; KEYENCE).

Statistical Analysis

Mann–Whitney U test was performed to determine the significance of differences in migration or gene expression using the Statistica software version 9.0 (StatSoft, Tulsa, Okla). Descriptive statistics are presented as mean \pm SD. The threshold for statistical significance was set at a *P* value less than 0.05. Each experiment was conducted in triplicate.

RESULTS

Decorin Expression Was Lower in E16 Wounds

Immunohistochemical staining demonstrated that decorin was widely expressed in normal murine embryo flank skin. Decorin immunofluorescence was of a relatively low intensity in regenerating E16 dermis postinjury (Fig. 1). In contrast, decorin was abundantly expressed at the base of E17 wounds. As the healing process progressed, diaminobenzidine staining demonstrated accumulation of decorin-expressing cells in E17 wound centers (Fig. 2). No such expression pattern was observed for E16 wounds.

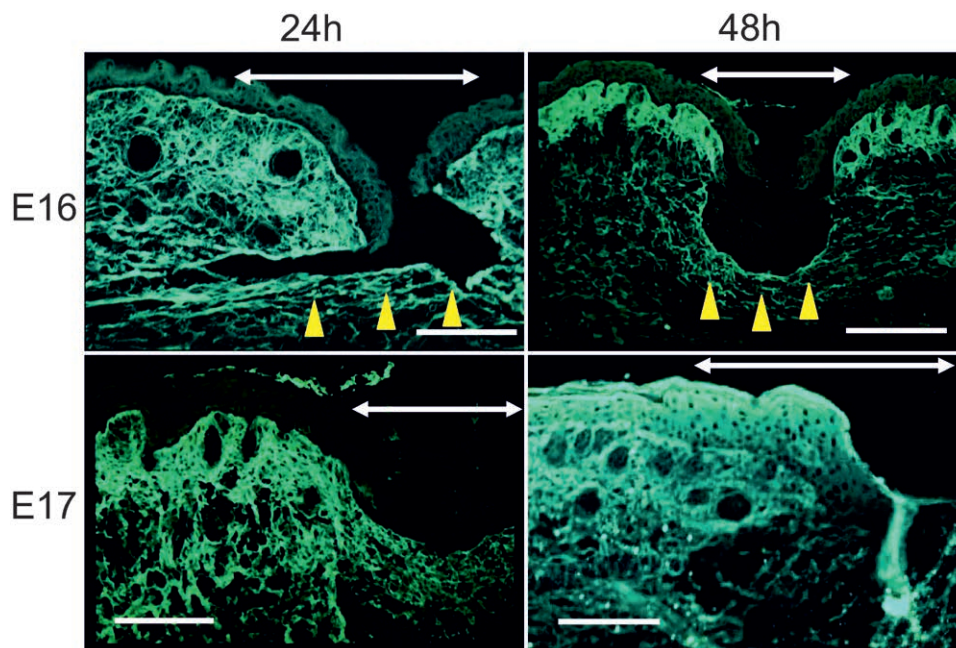


Fig. 1. Fluorescent immunostaining of decorin within injured E16 and E17 murine flank skin at 24 and 48 hours postinjury. Decorin was detectable at low levels at the E16 wound base (yellow arrows) and at higher levels at the E17 wound base. Wound breadth is indicated by double-sided white arrows. Scale bar = 100 μm .

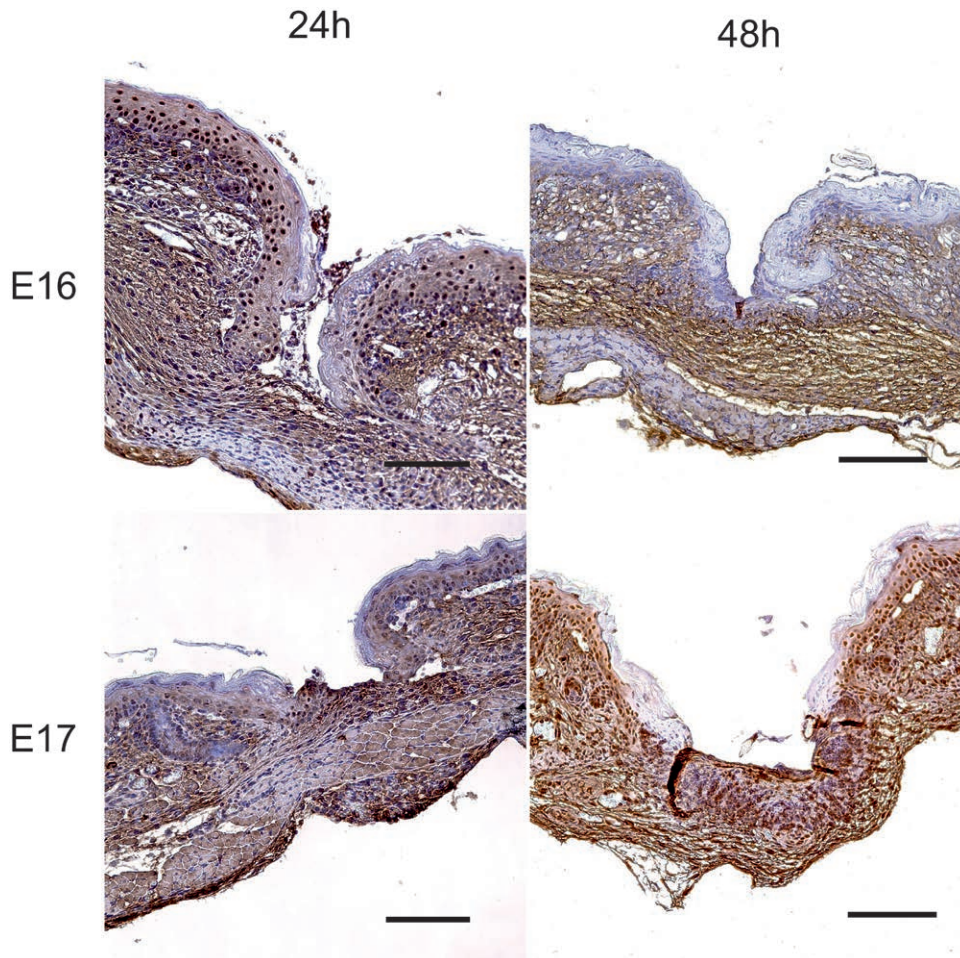


Fig. 2. 4',6-Diamidino-2-phenylindole immunostaining of decorin within injured E16 and E17 murine flank skin at 24 and 48 hours postinjury. Low levels of decorin were detectable within the E16 wound, and multiple decorin-expressing cells were concentrated within the center (area circumscribed by yellow lines) of the E17 wound. Scale bar = 100 μ m.

These findings indicated that dynamic postinjury decorin expression patterns were distinct at each embryonic stage and suggested a relationship between reduced expression after E16 injury and dermal regeneration.

Changes in Decorin Gene Expression during Embryonic Wound Healing

Consistent with the above findings, reverse transcription quantitative polymerase chain reaction demonstrated significantly lower postinjury E16 decorin transcription (0.41 ± 0.011 , $P \leq 0.05$) compared with normal skin at 24 hours after injury. At 48 hours, analysis of transcription differences suggested the decreased decorin levels in E16 skin were maintained (0.43 ± 0.011 , $P \leq 0.05$). Moreover, E17 decorin transcription at 24 hours postinjury was initially decreased (0.68 ± 0.12 , $P \leq 0.05$), albeit to a lesser degree than that in E16 skin. Decorin expression increased (1.23 ± 0.28), although not significantly, compared with that in normal skin at 48 hours postinjury (Fig. 3). This suggested that decorin expression may have recovered by 48 hours after injury of E17 embryos, unlike E16 embryos, which maintained lowered decorin levels after injury.

Decorin Inhibited Dermal Mesenchymal Cell Migration In Vitro

Boyden chamber assays demonstrated that fibronectin-induced migration of dermal mesenchymal cells derived from embryos injured at E17 was inhibited in a concentration-dependent manner by the presence of decorin (Fig. 4). The number of migrating cells was significantly decreased in the presence of high concentrations of decorin (90.0 ± 3.78 versus 8.67 ± 1.76 , $P = 0.004$). By contrast, fascial mesenchymal cell migration was unaltered by the presence of decorin (Fig. 5). Similarly, scratch assays demonstrated that decorin suppressed dermal mesenchymal cell migration (Fig. 6) but not fascial mesenchymal cell migration (Fig. 7), mimicking the process of scar tissue formation. These findings suggested that decorin differentially inhibited migration in a cell-specific manner.

DISCUSSION

Although decorin is known to be associated with wound healing in various organs (including adult skin), its expression dynamics during wound repair are highly complex and tissue-dependent.¹¹ Moreover, the exact

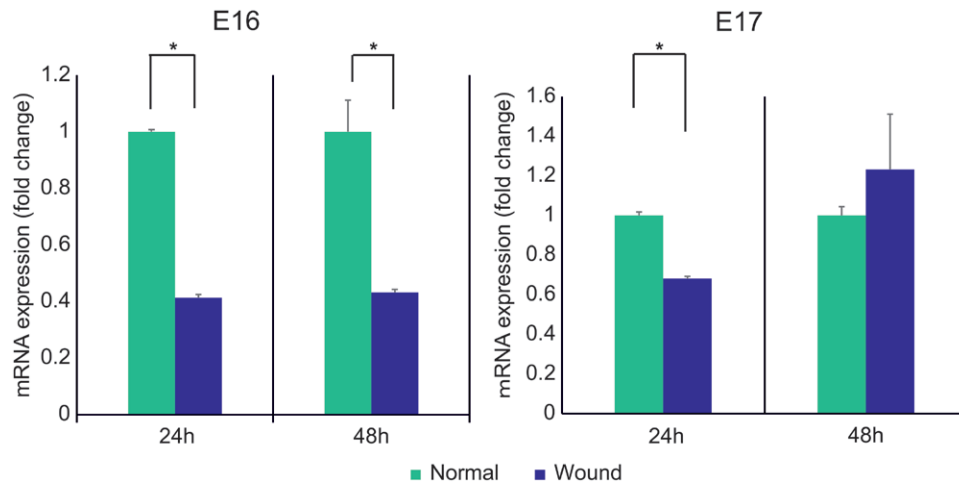


Fig. 3. Comparison of decorin transcript levels in wounded vs normal flank skin of E16 and E17 mice.

mechanisms through which decorin affects skin wound healing remain unknown.

It has also been reported that the expression of decorin in embryonic mice shows a distinct progressive pattern of expression.¹² In the early stages (E11), decorin was detectable only in the floor plate region. Later, at E13–16, decorin expression was particularly prominent in the pericardium, pleura, inner layers of the meninges and mesothelium of body cavities, and in the dermis and

subepithelium of the intestine and bladder. In contrast, the major parenchymal organs were only slightly positive for decorin. These findings suggest that decorin may play a role in epithelial/mesenchymal interactions during organ development and formation, but its contribution to wound healing was unclear.

Furthermore, during both adult and embryonic wound healing, durable scarring occurs owing to wound infiltration by fibroblasts normally residing proximal to loose

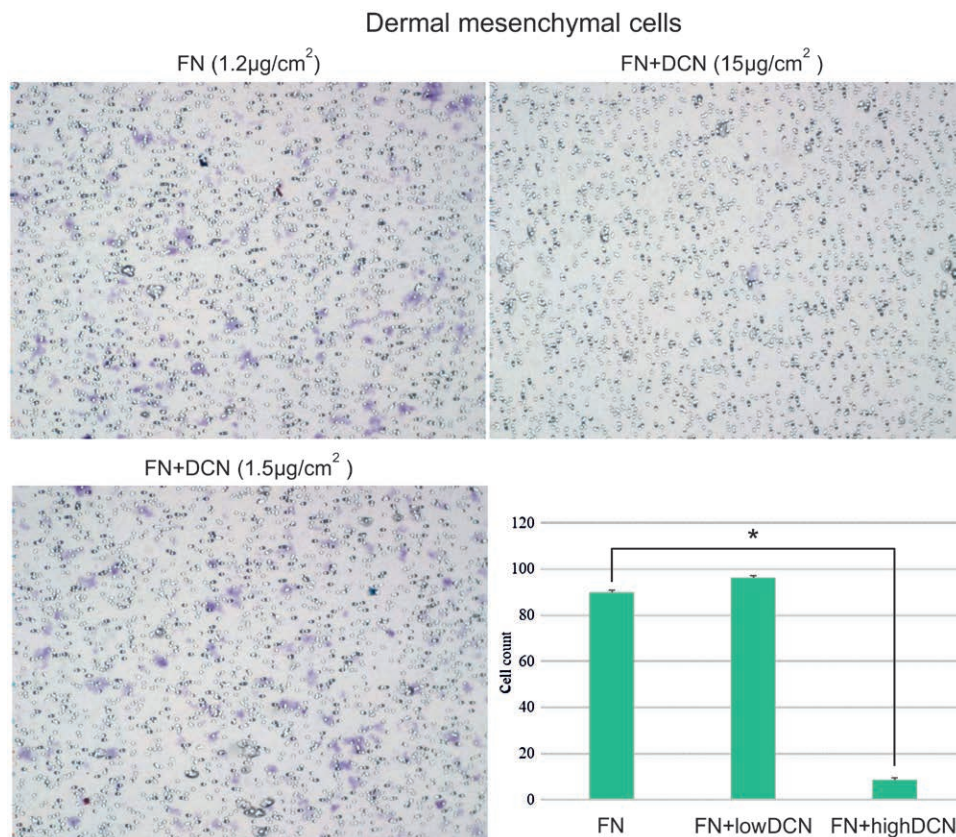


Fig. 4. Boyden chamber assays using E17 dermal mesenchymal cells. DCN: decorin; FN: fibronectin.

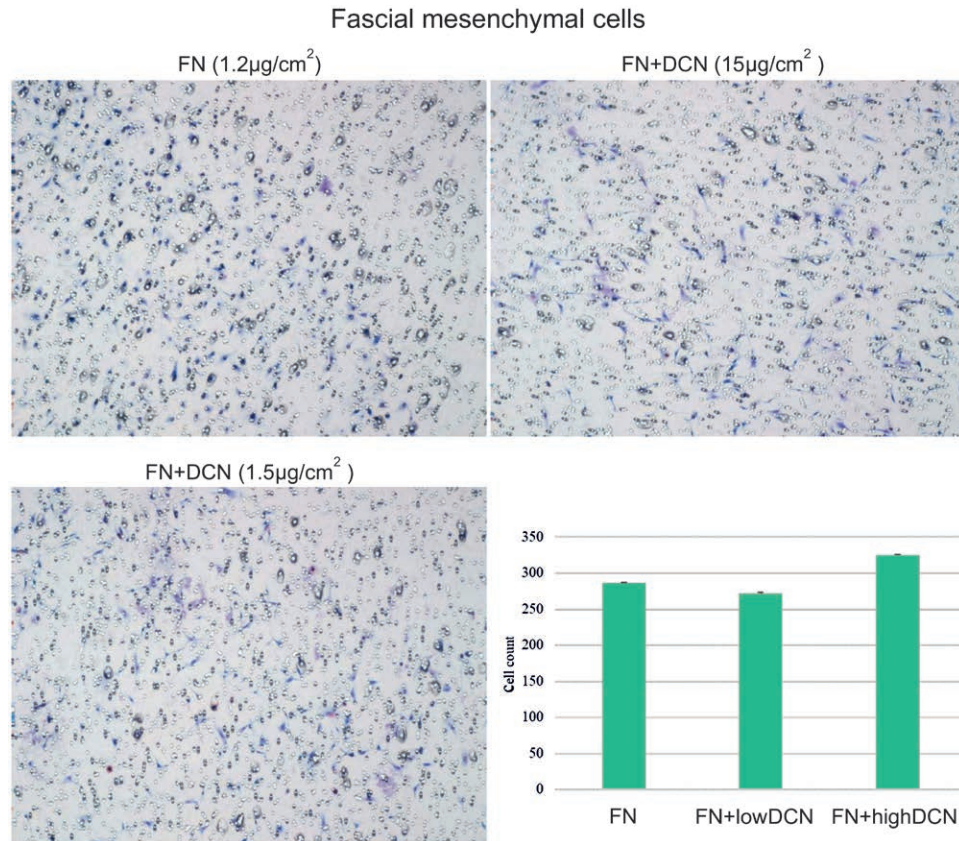


Fig. 5. Boyden chamber assays using E17 fascial mesenchymal cells.

fascia; however, both dermal mesenchymal cells and fibroblasts are important in the process of skin regeneration.^{4,13} The factors governing the dynamic behaviors of these cells during skin regeneration have not been characterized.

In this study, we demonstrated that levels of decorin transcription and expression were lower during flank skin wound healing in E16 mice, concomitant with complete regeneration and lack of scar formation. Moreover, we observed higher levels of decorin transcription and expression during flank skin wound healing in E17 mice, concomitant with incomplete regeneration and the presence of scarring. A recent analysis of decorin expression during adult skin wound healing also demonstrated that decorin expression becomes significantly upregulated in the first 3 days postinjury. In addition, in rat wound healing, decorin is similarly upregulated following late fetal (E18) or adult injury, in temporal association with upregulated fibroblast gene expression.¹¹ Our data are consistent with these reports and suggest an association between healing with scarring and high expression levels of decorin, from late embryonic stages to adult animals.

Decorin is also fundamentally important during the process of wound repair and in foreign body reactions. Indeed, wound healing is prolonged, and angiogenesis is enhanced in decorin-deficient mice.¹⁴ Therefore, researchers in the future may wish to use decorin-neutralizing antibodies in an attempt to enhance adult skin

wound healing, mimicking the lower levels of decorin expression observed during scarless embryonic wound healing (rather than attempting complete decorin depletion or blockade).

As demonstrated in the current study, the absence of detectable wound-site decorin co-occurred with dermal cell migration in E16 mice, whereas the presence of wound-site decorin co-occurred with dermal mesenchymal cell nonmigration in E17 mice, suggesting that dermal mesenchymal cell migration may be inhibited by decorin. Indeed, many studies have shown that decorin is associated with altered cell migration. For example, decorin inhibits the migration of endothelial cells in the MG-63 human osteosarcoma cells and MDA-MB-231 human epithelial breast carcinoma cells.^{1,15} Furthermore, knockdown of decorin in mouse embryonic fibroblasts enhances their cell migration ability.¹⁶ In the current study, both Boyden chamber and cell scratch migration assays demonstrated that decorin inhibited dermal mesenchymal cell migration in a concentration-dependent manner. By contrast, fascial mesenchymal cell migration was not inhibited by decorin. These differential cell type-specific effects on migration may help explain the mechanisms underlying the phenomenon of embryonic wound healing. Both E16 and E17 wound sites exhibit fascial mesenchymal cells during the early stages of wound healing, but only in E16 wounds do dermal mesenchymal cells later access the area below the re-epithelialized epidermis.^{3,4} However, in adult

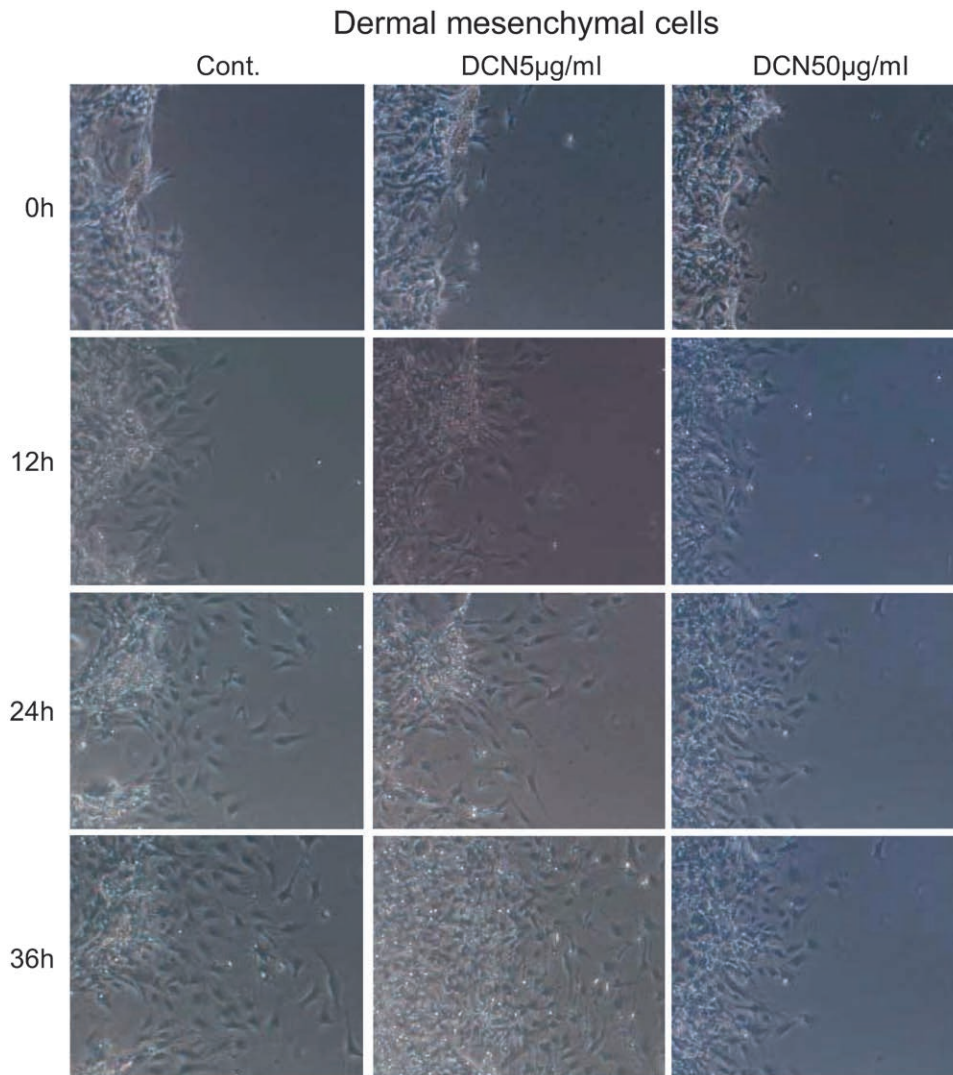


Fig. 6. Scratch assay using E17 dermal mesenchymal cells.

wounds, scar tissue is constructed by fascial rather than dermal mesenchymal cells.^{3,4,13,17} If the migration of both dermal and fascial mesenchymal cells was inhibited by decorin, mesenchymal cells would not bridge the wound site, and wound healing would be impaired.

To understand why decorin expression affects wound healing, we need to focus on decorin-related molecules. Decorin is degraded, at least in vitro, by matrix metalloproteinases (MMPs)-1, -2, -3, and -7, and several reports have shown that MMP-1 expression is elevated within embryonic wounds, suggesting a relationship between embryonic wound healing and MMPs.¹¹ Rebuilding of the extracellular matrix by MMPs is important in scar suppression, since scarless wounds are usually achieved by restoring collagen similar to that in the skin. However, our current analysis did not demonstrate immunohistochemical evidence for expression of such MMPs in healing E16 and E17 mouse flank skin wounds (data not shown).

Additionally, decorin can regulate the proliferation of tumor cells and skin fibroblasts by activating epidermal

growth factor receptor (EGFR) through EGFR-mediated receptor autophosphorylation and activation of downstream signaling pathways such as the mitogen-activated protein kinase 1/3 pathway.¹⁸ Furthermore, a recent study showed that decorin inhibited the migration of corneal parenchymal fibroblasts by inducing EGFR degradation.¹⁹ Further experiments are needed on EGFR degradation and dermal mesenchymal cell-specific migration inhibition induced by decorin.

Another molecular function of decorin is binding-dependent inhibition of transforming growth factor- β 1 (TGF- β 1).^{20,21} The pleiotropic cytokine TGF- β 1 is associated with promoting fibrosis. For example, TGF- β 1 induces fibrosis in the rabbit fetal wound model.²² Increased decorin expression during scar repair has thus been hypothesized to inhibit TGF- β activity²³; however, no studies have directly investigated the relationships between decorin expression and TGF- β 1 activity during skin development or repair. Exogenous TGF- β 1 was shown to promote scar formation in a human fetal cell model (partly by

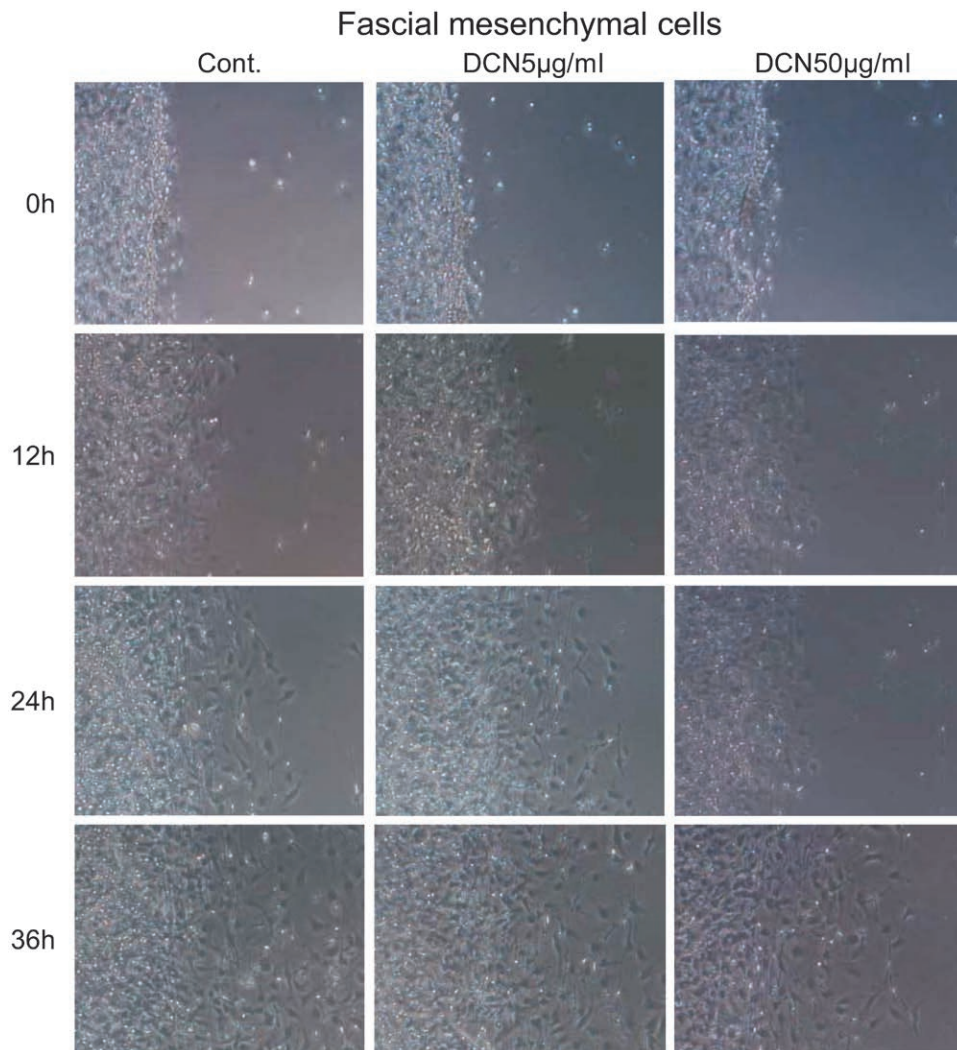


Fig. 7. Scratch assay using E17 fascial mesenchymal cells.

enhancing its own expression),²⁴ and the presence of TGF- β 1 is involved in scar formation.²⁵ Moreover, upregulation of TGF- β 1 promotes cell migration, and decorin has been reported to negatively regulate TGF- β expression,^{26,27} suggesting that inhibition of TGF- β activity is involved in the effect of decorin on the inhibition of dermal mesenchymal cell migration during wound healing. However, because mammals possess three TGF- β isoforms with unknown expression levels and decorin binding-affinities during wound healing,²⁸ it is not possible to confidently predict that altered decorin levels may affect TGF- β activity within embryonic wounds without further research. For example, studies are required to investigate the expression levels of each TGF- β isoform during wound healing.

A limitation of this study is the lack of *in vivo* evaluation of the effects of decorin suppression and enhancement on scar formation. However, decorin is involved in various factors other than wound healing, and simple knockdown, knockout, or overexpression is difficult to evaluate. In the future, we will investigate experimental methods to temporarily regulate decorin expression

only in the wound. In addition, it is necessary to confirm whether this phenomenon is applicable to mammals other than mice.

Based on our data showing a correlation between scarless skin regeneration in the developmental stages and low expression levels of decorin, if this could be mimicked in human skin or wound tissue, it would potentially help in the development of scarless wound healing and regenerative medicine.

CONCLUSIONS

During embryonic mouse flank skin wound healing, decorin expression was lower at E16 and higher at E17. The migration of dermal mesenchymal cells, which are involved in structural regeneration, was inhibited in the presence of decorin. Decreased expression of decorin may contribute to the phenotype of regeneration of dermal structures after wounding. Overall, our findings suggested that decorin downregulation may be a potential therapeutic strategy to enhance wound healing and prevent formation of scar tissue in adult skin.

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