Fascial fibroblast kinetic activity is increased during abdominal wall repair compared to dermal fibroblasts

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Abdominal wall fascial wound healing failure is a common clinical problem for general surgeons, manifesting in early postoperative fascial dehiscence as well as delayed development of incisional hernias. We previously reported that abdominal wall fascial incisions normally recover breaking strength faster than simultaneous dermal incisions in a rodent model. The accelerated fascial repair was associated with greater fibroblast cellularity within fascial wounds and increased wound collagen deposition. The current study was designed to determine whether accelerated fascial healing is the result of increased fascial fibroblast kinetic activity as measured by a more efficient fibroblast phenotype for binding to and remodeling a collagen matrix. Using a new model of abdominal wall repair, fibroblast cell cultures were developed from uninjured and wounded fascia and compared to dermal fibroblasts in order to define the fibroproliferative kinetic properties of abdominal wall fibroblasts. Fascial wound fibroblasts produced a more efficient and greater overall collagen lattice compaction compared to dermal fibroblasts. Acute fascial wound fibroblasts also showed enhanced cell proliferation compared to dermal fibroblasts but no significant differences in collagen production when normalized to cell number. These results suggest that fascial fibroblasts express distinct acute repair phenotypes and therefore a specific mechanism for fascial repair following injury. (WOUND REP REG 2004;12:539–545)

Recovery from all surgical procedures requires the timely reestablishment of injured tissue structure and function. Despite improvements in surgical techniques and peri-operative care, acute wound healing failure remains a frequent complication for all surgical disciplines.1 The failure of acute tissue repair in turn results in further morbidity and even mortality for the surgical patient. To date, the majority of wound healing studies have focused on the skin, and little is known about the unique soft tissue characteristics and healing mechanism of other abdominal wall components like the fascia. Anatomically, the abdominal wall fascia is less vascularized than dermis and collagen bundles are organized into predominately parallel orientation. Functionally, the fascia behaves more like ligaments and tendons while being subjected to greater mechanical stress than the dermis.2 The local wound environment is known to play an important role in tissue morphogenesis and repair following injury. Load forces exerted across the wound, for example, have been shown to significantly modulate repair fibroblast migration and maturation of the extracellular matrix.3-5 Given the distinct physiologic roles and different histologic architecture, it is likely that fascial repair fibroblasts are activated and function in a manner distinct from dermal fibroblasts. However, the mechanism for modulating the activation and distribution of fascial repair fibroblast infiltrative, proliferative, and synthetic activity during fascial wound healing is not completely understood.
We previously reported that abdominal wall fascial incisions recover breaking strength faster than simultaneous dermal incisions in a rodent model.\textsuperscript{6} This finding was consistent with data showing that load bearing soft tissues repair tissue injury faster than nonload bearing tissues.\textsuperscript{7} The accelerated fascial repair was associated with greater fibroblast cellularity within the fascial wounds and increased type I and III collagen expression in seven-day fascial wounds.\textsuperscript{6} These results suggest a more efficient fascial repair fibroblast infiltrative and/or proliferative response when compared to a dermal repair fibroblast. The current study was designed to determine whether accelerated fascial healing is the result of increased fascial fibroblast intrinsic kinetic activity as measured by a more efficient fibroblast phenotype for binding to and remodeling a collagen matrix. Fibroblasts cultured from uninjured and wounded fascia were compared to dermal fibroblasts to define the fibroproliferative kinetic properties of abdominal wall load bearing fibroblasts and dermal repair fibroblasts.

**MATERIALS AND METHODS**

Fifteen male Sprague Dawley rats weighing 275–300 g (Harlan Laboratories, Indianapolis, IN) were acclimated to laboratory conditions for seven days and fed a standard rat chow. All animal care and operative procedures were performed in accordance with the *United States Public Health Service Guide for the Care of Laboratory Animals* (NIH Publication Number 86–23, revised 1985) and were approved by the Ann Arbor Veterans Affairs Medical Center Institutional Animal Care and Use Committee. Following intraperitoneal injection of ketamine (87 mg/kg) and xylazine (13 mg/kg) for anesthesia, ventral abdominal wall hair was shaved with electric clippers and the field prepped with alcohol and betadine solution. A $6 \times 3$ cm full-thickness dermal incision was placed 2 cm lateral to the ventral midline and a rectangular skin flap was raised through the avascular prefascial plane, thereby separating the fascial and dermal wound healing environments. The 2:1 ratio of flap width to length prevents ischemic impairment of skin healing. A 5-cm full-thickness myofascial incision was then placed in the midline and closed with four interrupted 4–0 nylon sutures placed 3 mm from the cut edges and beginning 1 cm from the end of the incision. The skin flap was replaced and the dermal incisions closed with skin clips placed 1 cm apart. After 30 minutes of recovery under heat lamps, the rats were returned to individual cages.

Five rats served as unwounded controls and were euthanized by an overdose of nembutal (100 mg/kg ip). Fascial biopsies were taken from the linea alba of the midline abdominal wall and dermal biopsies were taken from the skin of the abdominal wall 2 cm lateral to the midline. Five rodents were randomly killed on postoperative days 7 and 14 by an overdose of nembutal. Biopsies were obtained from the healing fascial and dermal incisions.

**Fibroblast cell culturing**

Biopsies taken for fibroblast cell culture were placed in Dulbecco’s modified Eagle’s medium (DMEM, Gibco/BRL, Grand Island, NY), with 10 percent fetal bovine serum and 2 percent antibiotic solution containing 10,000 $\mu$/ml penicillin G, 25 $\mu$/ml amphotericin B, and 10,000 $\mu$/ml streptomycin sulfate solution (Gibco/BRL), and stored overnight at 4°C. The next day the wound biopsy specimens were cut into small 1–2 mm cubed pieces and placed in 60-mm culture plates containing Dispase solution (Collaborative Biomedical Products, Bedford, MA) for 15 minutes at 37°C. DMEM culture media was then slowly added to the culture dish, and the tissue samples were incubated at 37°C in 5 percent CO$_2$. The media was changed for fresh DMEM every three days, and the fibroblast primary cell cultures were grown to confluence. One million
fibroblasts were then subcultured and these first-passage fibroblasts were grown until >90 percent confluent. The fibroblasts were then subcultured a second time and the second-passage fibroblasts grown to confluency and harvested for qualitative morphologic assessment, fibroblast-populated collagen lattice compaction assays, proliferation studies, and collagen analysis.

**Fibroblast-populated collagen lattices**

Collagen lattices were prepared from type I rat tail collagen as described by the manufacturer (Upstate Biotechnology, Lake Placid, NY). Undiluted collagen was placed in sterile 35-mm cell culture dishes and spread evenly. The dishes were then placed in an ammonia vapor chamber for three minutes. The collagen was washed with sterile distilled water four times to remove excess ammonia and phosphate buffered saline solution with 1 percent fetal bovine serum was added. The collagen gel was then incubated for 24 hours at 4 ºC. The fibroblasts were counted and their cell number adjusted to \(1 \times 10^5\) cells/ml. One hundred thousand second-passage cultured fibroblasts were added to each prefabricated 3.5-cm collagen lattice. The collagen lattices were then incubated at 37 ºC in a humidified incubator with 5 percent CO\(_2\) and the extent of gel contraction measured every 24 hours for five days. The gels were digitally imaged each day and contraction measurements calculated using Sigma Scan software (Jandel Scientific, Corte Madera, CA). Samples were run in triplicate and the average results reported. Differences in lattice compaction were determined using ANOVA (SigmaStat, SPSS, Inc., Chicago, IL).

**Proliferation assessment**

Fibroblast proliferation was determined via the methylthiazol tetrazolium (MTT) cell proliferation assay (ATCC, Manassas, VA) and manual cell counting. The MTT assay was performed per the manufacturer’s instructions. Briefly, 100,000 second-passage fibroblasts were plated per well in a 96-well plate and incubated in fresh media for 24 hours. MTT reagent (10 µl) was added and the samples incubated for four hours at which time a purple precipitate became visible. Detergent reagent (100 µl) was added and the samples were left at room temperature in the dark overnight. The samples were read on a microtiter plate reader with a 570-nm filter. Samples were run in triplicate and the absorbance plotted against number of cells/ml generated in a standard curve to determine cell count. Results are reported as percent increase over baseline. Manual cell counting was performed by culturing 200,000 second-passage fibroblasts/well with fresh media in a six-well plate for 48 hours. The cells were then released with trypsin and counted manually with a hemocytometer. Samples were run in triplicate and the average cell count reported.

**Immunocytochemistry procedure**

Fibroblasts were plated into eight-well chamber slides (Nalge Nunc, Naperville, IL) and incubated at 37 ºC in 5 percent CO\(_2\) for five days. The fibroblast monolayer was washed, fixed with 2 percent formalin, dried with methanol, and stored at –20 ºC until staining. Rabbit polyclonal antibodies for vimentin (H-84), desmin (H-76), or pan cytokeratin (H-240) (Santa Cruz Biotechnology, Santa Cruz, CA) were incubated with the cells for one hour. The Vectastain Elite ABC kit (Vector Laboratories, Burlingame, CA) was used then used for staining with a DAB peroxidase substrate solution. The slides were evaluated by an observer blinded to treatment and qualitatively graded as positive if over 95 percent of the cells shown staining or negative if less than 5 percent showed staining.

For examination of collagen and α-smooth muscle actin, fibroblasts were plated into eight-well chamber slides, incubated for five days, then fixed and stored at –20 ºC until staining. Polyclonal antibodies for type I collagen (M-19), type III collagen (C15) (Santa Cruz Biotechnology), and anti-rat smooth muscle actin (Chemicon International Inc., Temecula, CA) were used with the Vectastain Elite ABC kit as described above. The fibroblasts were digitized using an Eclipse E400 microscope with a SPOT digital camera attachment. The intensity of staining at each timepoint was recorded in three high-powered fields by an observer blinded to treatment. The intensity of staining was quantified using SigmaScan Pro v 4.01 (SPSS, Inc., Chicago, IL) imaging software. Differences in staining intensity of samples compared to an unstained standard were determined using ANOVA.

**Total collagen assay**

Intracellular collagen levels were measured using the Sircol collagen assay method (Accurate Chemical and Scientific Corp., Westbury, NY). One million second-passage fibroblasts were counted with a hemocytometer, washed with DMEM, and pelleted in a microcentrifuge tube. The supernatant was discarded and 200 µl of Complete protease inhibitor cocktail (Roche Applied Science, Indianapolis, IN) in phosphate buffered saline solution with 0.5 percent Triton X-100 (Sigma-Aldrich, St. Louis, MO) was added and the pellet dissolved. After centrifugation at 14,000 rpm for 15 minutes, 100 µl of the supernatant was added to 1000 µl of Sircol dye reagent and incubated at room temperature for 30 minutes. The specimen was then centrifuged at 14,000 r.p.m. for 15 minutes and the supernatant was completely drained off and discarded. One thousand microliters of 0.5 M NaOH
was added to the collagen-bound dye pellet to release the bound dye into solution. The OD of each sample was determined with a microplate reader at 560 nm. Results were recorded as micrograms of total collagen per million fibroblasts.

RESULTS

All animals tolerated the surgical protocol without death or apparent complications. At necropsy, there was no evidence of dermal or fascial dehiscence, infection, flap necrosis, or any fluid collections.

Primary cell cultures were generated from dermal and fascial tissue explants. All cells stained positive for vimentin, a marker of mesenchymal-derived cells. In contrast, cell staining was negative for desmin, a skeletal muscle cell marker, and negative for pan-cytokeratin, a marker for keratinocytes and other epithelial-derived cells. Microscopic morphologic evaluation revealed elongated spindle shaped cells with numerous cytoplasmic processes. The intermediate filament staining pattern and cell morphology suggests that the primary cell cultures were nonskeletal muscle mesenchymal cells, consistent with a fibroblast lineage.

Collagen lattice compaction was compared in matrices seeded with fascial or dermal fibroblasts derived from unwounded tissue, 7-day, or 14-day wounds (Figure 2). In both the fascia and dermis, fibroblasts cultured from acute wounds caused significantly more lattice compaction during the first 24 hours of the FPCL assay than fibroblasts cultured from uninjured tissue. The increased fibroblast kinetic activity was most pronounced in fibroblasts derived from seven-day wounds in both the fascia and dermis. The majority of the enhanced wound fibroblast collagen lattice compaction occurred in the first 24–48 hours. In contrast, unwounded FPCL contraction slowly progressed throughout the study period in both the dermis and fascial fibroblasts. Final compaction at day 5 was comparable between the unwounded and wounded fibroblasts in both the dermal and fascial specimens.

Fibroblasts cultured from unwounded fascia and acute fascial wounds were more efficient in causing lattice compaction and caused a greater overall lattice compaction when compared to unwounded dermis and acute dermal wound fibroblasts (Table 1). Unwounded fascial fibroblasts achieved 55 percent of maximal compaction after 24 hours while unwounded dermal fibroblasts achieved only 28 percent maximal compaction. After five days, the seven-day fascial fibroblasts achieved a 28 percent greater lattice compaction than seven-day dermal fibroblasts. The rate of collagen matrix compaction caused by fibroblasts cultured from unwounded fascia was comparable to the rate of collagen matrix compaction caused by dermal fibroblasts cultured from seven-day wounds.

There was no significant modulation of α-smooth muscle actin staining in acute wound or unwounded control fibroblast cultures (data not shown). Similarly, there were no significant differences observed in α-smooth muscle actin staining between fascial or dermal wound fibroblasts over the entirety of this early, acute wound time course. The relatively uniform expression of α-smooth muscle actin staining suggests that the differences in FPCL compaction were not a function of a larger population of myofibroblasts.

![Graph A](image1.png)  ![Graph B](image2.png)

**FIGURE 2.** Collagen lattice compaction was measured over five days using matrices seeded with cultured dermal and fascial fibroblasts derived from unwounded tissue, 7- or 14-day wounds. (A) Dermal fibroblasts; (B) fascial fibroblasts. Fibroblasts cultured from fascia were more efficient in causing lattice contraction and induced greater overall matrix compaction when compared to dermal fibroblasts. Fibroblasts cultured from 7- and 14-day wounds caused significantly more lattice contraction during the first 24 hours of the FPCL assay than fibroblasts cultured from uninjured fascia or dermis. Significance was tested with ANOVA. *p<0.05, **p<0.01 day 7 wound vs. unwounded; +p<0.05 day 14 wound vs. unwounded.
Cell proliferation was significantly increased in the seven-day fascial fibroblast cell cultures compared to dermal fibroblasts (Table 2). Metabolic proliferation assays revealed a 44.8 percent increase over baseline in the seven-day fascial fibroblasts compared to a 6.4 percent increase in the seven-day dermal wound fibroblasts. Manual cell counts revealed similar trends in the seven-day wound fibroblast cultures. Fascial fibroblast proliferation decreased between the 7- and 14-day wound fibroblast cultures. By the 14-day wound time-point, fascial fibroblast cell proliferation rates were equivalent to the dermis.

Collagen production appeared to be significantly increased in seven-day fascial wound fibroblasts via semiquantitative immunocytochemistry evaluation (Figure 3). Both type I and III collagen staining intensity was significantly increased in seven-day wound fascial fibroblast cell cultures compared to uninjured controls (type I collagen intensity: 88 ± 6 vs. 64 ± 4, p < 0.01; type III collagen intensity: 106 ± 7 vs. 66 ± 3, p < 0.01). Fourteen-day wound fascial fibroblast types I and III collagen levels returned to near baseline unwounded levels. In contrast, types I and III collagen levels remained relatively consistent in the unwounded and wounded dermal fibroblast cell cultures. However, biochemical analysis of total collagen content per one million fibroblasts was remarkably similar across timepoints. The total collagen content normalized to one million fibroblasts derived from fascia compared to dermis was 31.5 μg ± 2.8 vs. 29.0 μg ± 4.9 (p = NS). This suggests that the increased collagen levels in the seven-day wound fascial fibroblasts observed via immunocytochemistry evaluation may be due to the enhanced cell proliferation at this timepoint. Retrospective qualitative evaluation of the seven-day wound fascial fibroblast collagen staining confirmed greater cellularity present at this timepoint (Figure 2B).

**DISCUSSION**

This study measured phenotypic differences between fascial-derived and dermal-derived fibroblasts in both wounded and unwounded tissue. Significant phenotypic variations are isolated in fibroblasts derived from different embryologic sources. Dermal fibroblasts isolated from different areas of the body have been shown to have distinct gene expression profiles which correlate with dermal disease processes specific to certain anatomic regions. The concept of distinct fibroblast phenotypes is consistent with our in vivo observations that the initiation and progression of recovery of wound tensile strength in acute fascial wounds occurs earlier than in the dermis. This finding suggests that a surgically created full-thickness abdominal wall incision has unique wound healing environments at the fascial and dermal levels with differential rates and modes of recovery of native structure and function.

To better study and compare abdominal wall fascial and dermal acute wound healing, we developed an animal model that separates these two wound healing environments. A dermal "trap-door" rectangular paramedian skin flap was raised through the avascular prefascial plane, and a full-thickness fascial incision made through the linea alba (Figure 1). The incisions were closed and allowed to heal, anatomically separated by 1 or 2 cm. A 2:1 dermal flap width-to-length ratio was maintained to prevent flap ischemia and necrosis. Prior studies showed the paramedian dermal incision has equivalent blood supply and recovers breaking strength equivalent to a midline dermal incision. In this model,

### Table 1. Collagen lattice compaction measured in vitro over five days using matrices seeded with dermal and fascial fibroblasts cultured from unwounded tissue, 7- or 14-day wounds

<table>
<thead>
<tr>
<th>Wound age</th>
<th>Cell origin</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
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<tr>
<td>Unwounded</td>
<td>Skin</td>
<td>7.1 ± 4.3*</td>
<td>16.0 ± 4.7</td>
<td>22.1 ± 1.0</td>
<td>24.5 ± 0.6</td>
<td>25.1 ± 0.9</td>
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<tr>
<td></td>
<td>Fascia</td>
<td>24.5 ± 6.5</td>
<td>28.2 ± 2.8</td>
<td>31.5 ± 8.8</td>
<td>38.6 ± 6.9</td>
<td>44.8 ± 6.0</td>
</tr>
<tr>
<td>7-day wound</td>
<td>Skin</td>
<td>24.4 ± 1.8</td>
<td>24.8 ± 4.4</td>
<td>28.9 ± 2.9</td>
<td>29.1 ± 8.5</td>
<td>32.4 ± 5.0</td>
</tr>
<tr>
<td></td>
<td>Fascia</td>
<td>38.5 ± 4.9</td>
<td>41.1 ± 4.7</td>
<td>41.3 ± 5.9</td>
<td>41.4 ± 3.1</td>
<td>41.6 ± 5.6</td>
</tr>
<tr>
<td>14-day wound</td>
<td>Skin</td>
<td>16.3 ± 1.8</td>
<td>25.2 ± 1.8</td>
<td>25.4 ± 1.4</td>
<td>25.6 ± 9.5</td>
<td>27.8 ± 3.9</td>
</tr>
<tr>
<td></td>
<td>Fascia</td>
<td>21.8 ± 3.2</td>
<td>30.5 ± 5.4</td>
<td>33.3 ± 5.8</td>
<td>34.9 ± 4.2</td>
<td>36.2 ± 7.5</td>
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</table>

*Values are the mean ± standard deviation. Significance was tested with ANOVA.

### Table 2. Cell proliferation measured by the MTT assay and manual cell counting

<table>
<thead>
<tr>
<th>Proliferation method</th>
<th>Cell origin</th>
<th>7-day wound</th>
<th>14-day wound</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTT* (Percent increase)</td>
<td>Skin</td>
<td>6.4% ± 3.7**</td>
<td>5.0% ± 1.9</td>
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<tr>
<td></td>
<td>Fascia</td>
<td>4.9% ± 15.7</td>
<td>9.6% ± 2.6</td>
</tr>
<tr>
<td>Manual count+ (Cell number)</td>
<td>Skin</td>
<td>1.44 ± 0.056 × 10^6</td>
<td>1.32 ± 0.024 × 10^6</td>
</tr>
<tr>
<td></td>
<td>Fascia</td>
<td>1.67 ± 0.075 × 10^6</td>
<td>1.38 ± 0.049 × 10^6</td>
</tr>
</tbody>
</table>

* MTT values indicate % change increase.
** Values are the mean ± standard deviation. Significance is tested with t-test.
+ Manual count values indicate cell number.
fascial and dermal acute wound biology can be studied within the same rat, thus controlling for the surgical stress and other biologic and environmental variables.

The collagen lattice compaction studies showed that fascial derived fibroblasts induced a more efficient and greater overall contraction of a fibroblast-populated collagen lattice than dermal derived fibroblasts. The enhanced fascial fibroblast kinetic activity was showed at all timepoints. Fibroblasts cultured from acute fascial or dermal wounds caused significantly more lattice contraction than fibroblasts cultured from unwounded tissue. The seven-day acute wound fibroblasts were most efficient at compaction of FPCLs in both dermal and fascial derived cultures. The rate of lattice compaction by uninjured fibroblasts was nearly constant (i.e., no significant log phase), whereas wounded fibroblasts induced a rapid reduction in the surface area of the FPCL’s during the first 24 hours.

There were no significant variations in $\alpha$ smooth muscle actin staining in the dermal or fascial fibroblasts, nor were there any major differences between unwounded or wounded fibroblasts. The uniform staining suggests that an actin-rich myofibroblast contraction mechanism does not account for the increased kinetic potential in wounded vs. unwounded fibroblasts. The mechanism appears to be more consistent with Ehrlich’s hypothesis that moderate density FPCL lattice contraction is a function of collagen fiber reorganization that in turn is dependant upon independent fibroblast locomotion. Fibroblasts suspended in the collagen lattice matrix reorient the surrounding collagen fibrils and bundles, theoretically in accordance with their dermal or fascial phenotype of origin. In vivo, dermal collagen bundles are arranged in a complex basket weave arrangement as opposed to fascia, where collagen bundles are arranged in a more simple parallel manner along lines of tension. Native tissues with collagen bundles organized in a parallel orientation, as in fascia, ligament, or tendon, regain breaking strength faster than dermal tissue with a three-dimensional fiber network.

Stimulated fascial fibroblast fibroproliferative ability was concordant with the observed increased kinetic function. There was a significant increase in fibroblast proliferation rates in the 7-day wound fascial fibroblasts followed by a decrease in the 14-day wound fibroblasts. In contrast, the proliferation rate of dermal fibroblasts was relatively uniform. Types I and III collagen deposition also appeared to be significantly increased in the seven-day wound fibroblasts based on semi-quantitative immunocytochemistry. However, the cell culture methodology for immunocytochemistry did not control for the 36 percent enhanced proliferation rate of the seven-day wound fascial fibroblasts. Biochemical analysis of total collagen content per one million cells confirmed that the distribution of intracellular collagen was equivalent across timepoints. The local fascial wound environmental advantage thus appears to be primarily a proliferative influence as opposed to enhanced intrinsic collagen production. These in vitro fibroblast data are consistent with increased in vivo fibroblast...
cellularity and total collagen deposition in postoperative fascial compared to dermal wounds.6

The rapid FPCL contraction and enhanced proliferation suggests that acute wound repair fibroblasts are “primed,” mediating enhanced fibroblast kinetic activity. Endogenous local soluble growth factors induced by tissue injury stimulate fibroblast kinetic activity and are at high tissue concentration12 during this timepoint of maximal fibroblast-mediated matrix contraction. The uninjured tissue milieu, in contrast, does not express elevated soluble repair signals like cytokines and growth factors. Other studies have shown that the addition of noncellular wound fluid can significantly increase contractile properties of uninjured fibroblasts, suggesting that the local wound environment is an important regulator of fibroblast phenotype.13 Enhanced lattice compaction may also be mediated by the upregulation of cell surface integrin receptors or other molecules responsible for fibroblast: provisional matrix interactions in acutely wounded fibroblasts.14

In summary, we originally observed that abdominal wall fascial incisions recover breaking strength faster than simultaneous dermal incisions in a rodent model.5 The accelerated fascial repair was associated with greater in vivo fibroblast cellularity within the fascial wounds and increased type I and III collagen expression. This study suggests that in vitro baseline fibroblast kinetic activity is greater in the fascia compared to the dermis, and fascial fibroblasts showed a more robust response to acute wound signals. Fascial fibroblasts cause a more efficient and greater overall collagen lattice contraction and showed an enhanced cell proliferation compared to the dermis. Clinically this translates into a fibroblast phenotype resulting in a more efficient fascial tissue-specific repair.

ACKNOWLEDGMENTS

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REFERENCES