HHS Public Access

Author manuscript

Curr Opin Pediatr. Author manuscript; available in PMC 2015 August 07.

Published in final edited form as:

Curr Opin Pediatr. 2012 June ; 24(3): 371–378. doi:10.1097/MOP.0b013e3283535790.

Fetal wound healing: implications for minimal scar formation

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Abstract

Purpose of review—The mid-gestation fetus is capable of regenerative healing with wound healing indistinguishable from surrounding skin. This review aims to evaluate the current knowledge of how the mid-gestation fetus heals without scar and the implications of these findings in efforts to recapitulate the fetal regenerative phenotype in the postnatal environment.

Recent findings—It has been over 30 years since the empirical observation that the fetus heals without scar; yet, the underlying mechanisms of this phenomenon have not been elucidated. Fetal wound healing is characterized by a distinct growth factor profile, an attenuated inflammatory response with an anti-inflammatory cytokine profile, an extracellular matrix rich in type III collagen and hyaluronan, attenuated biomechanical stress, and a potential role for stem cells. Current therapies to minimize scarring in postnatal wounds have attempted to recapitulate singular aspects of the fetal regenerative phenotype and have met with varying degrees of clinical success. We now have the molecular tools to more completely comprehend the fundamental mechanisms of fetal regenerative wound repair, which has the potential to provide insights into the identification of therapeutic targets to minimize the scar formation.

Summary—Successful therapies that help minimize postnatal scar formation can be realized through understanding the cellular and molecular mechanisms of fetal regenerative wound healing. These insights will have implications not only for cutaneous wound healing, but also potentially for any disease process characterized by excessive fibroplasia.

Keywords

fetal wound healing; hyaluronan; interleukin-10; scar formation

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Conflicts of interest

There are no conflicts of interest.

INTRODUCTION

The economic and social impact of scarring is significant. Each year over 100 million patients acquire scars, some of which cause considerable functional or psychosocial morbidity [1, 2]. Additionally, there are an estimated 11 million keloid scars and 4 million burn scars, 70% of which occur in children [3]. An effective therapy resulting in scarless wound healing would have an extraordinary impact across many fields of medicine.

Wound healing is a complex process that normally occurs in the postnatal setting through the formation of scar tissue, with regenerative healing limited to the liver and bone [4]. In contrast, the fetus is known to heal cutaneous wounds without a scar by regeneration of normal dermal architecture including restoration of dermal appendages and neurovasculature [5, 6▪]. This regenerative capability occurs in the mid-gestational period and has been demonstrated in all mammalian species studied to date, including humans, mice, rats, sheep, and monkeys. In each fetal model, this period of regenerative healing is followed by a transition period in which wounds heal with an extracellular matrix (ECM) indistinguishable from unwounded tissue, but fail to regenerate its dermal appendages [7]. Near the end of gestation, there is a progression to the postnatal phenotype with wounds healing with an excess of collagen in the ECM, a loss of dermal appendages, and a flattened epidermis in what we classify as a scar.

Early studies in the biology of fetal wound healing have focused on the intrauterine wound environment. The sterile, nutrient-rich amniotic fluid, which continuously bathes the fetal skin, was believed to have an important role in fetal wound phenotype. A number of animal studies suggest that fetal regenerative repair is independent of the intrauterine environment. For example, wounds in the marsupial model, in absence of amniotic fluid, heal without scar formation during the period of development within the maternal pouch [8]. Furthermore, studies in wounds created in human mid-gestation fetal skin following xeno-grafting to immunocompromised adult mice showed scarless wound healing [9]. Conversely, incisional wounds in adult sheep skin engrafted to fetal lambs and returned to the in-utero environment were noted to heal with scar formation [10]. These findings suggest an intrinsic property of fetal skin that is permissive of scarless wound healing and independent of the in-utero environment.

A more complete understanding of the fundamental mechanisms of fetal wound healing will identify the therapeutic targets with the capacity to minimize scar formation. This goal has obvious implications for cutaneous wound healing, but also has potential for any disease characterized by increased fibroplasia, such as intra-abdominal adhesions, keloids, scleroderma, pulmonary and renal fibrosis, and hepatic cirrhosis. Current studies have focused on the cellular and molecular aspects of fetal wound healing to elucidate the mechanisms of fetal regenerative wound healing and can be divided into five major categories: growth factors; inflammatory response and cytokines; ECM; mechanical stress; and stem cells (Table 1). The purpose of this review is to describe the biologic basis of the fetal phenotype in order to apply these physiologic principles to recapitulate the scarless wound healing phenotype in postnatal tissue repair.

GROWTH FACTORS

A variety of growth factor families are believed to play a role in fetal wound healing. Much of this research has been centered on transforming growth factor (TGF)-β and its three mammalian isoforms (TGF-β1, TGF-β2, and TGF-β3). TGF-β is secreted by many cell types involved in tissue repair [11]. In adult wounds, there is a relative increase in the expression of TGF-β1 and TGF-β2 compared with TGF-β3. In contrast, fetal wounds express more TGF-β3 and decreased levels of TGF-β1 and TGF-β2. Pathologic hypertrophic scars in adults have been noted to have even higher levels of TGF-β1. Further, functional inhibition of TGF-β1 in adult wounds significantly reduces scarring. Conversely, addition of recombinant TGF-β1 to mid-gestation fetal wounds results in the formation of scar tissue [12]. These data suggest low levels of TGF-β1 are associated with decreased scarring. Additional studies have suggested that, beyond the relative paucity of TGF-β1, elevated levels of TGF-β3 and a higher ratio of TGF-β3 to TGF-β1 may also be critical to decreasing scar formation [13]. Studies in postnatal wounds have demonstrated reduced scarring with addition of recombinant TGF-β3 and increased scarring with attenuation of TGF-β3 levels [14]. In addition, treatment of adult fibroblasts with TGF-β3 has demonstrated increased migration, a characteristic of fetal fibroblasts [15].

These promising studies in animal models prompted the development of Avotermin, human recombinant TGF-β3, as a potential antiscarring therapy. Avotermin was evaluated in multiple randomized, double-blinded, placebo-controlled, phase II clinical trials with administration immediately prior to and 24h following wounding. It was found to improve scar appearance compared with placebo [16▪▪]. Unfortunately, phase III trials of Avotermin were terminated as the therapy failed to meet its primary endpoint of decreasing scar formation [17]. Interestingly, the recombinant TGF-β3 was administered in the immediate perioperative period, with effects on scarring noted months later. This highlights a potential critical early window in postnatal wounds that may be amenable to manipulation that will provide a permissive environment for scarless wound healing to proceed.

Another TGF-β inhibitor, mannose-6-phosphate (M6P), has also been evaluated as a scar-reducing therapy. Phase II trials have demonstrated accelerated cutaneous wound closure and decreased erythema [18]. Evaluation of M6P as a scar-reducing therapy in applications beyond cutaneous wound repair, such as following nerve repair, is currently being evaluated [19].

INFLAMMATORY RESPONSE AND CYTOKINES

A hallmark of the fetal regenerative phenotype is an attenuated inflammatory response. This is observed in decreased inflammatory cellular infiltrate, as well as a characteristic expression of cytokines, the mediators of the inflammatory response.

Inflammatory cells

The infiltration of neutrophils which characterizes the early postnatal wound is greatly diminished in fetal wounds [5]. The number of tissue macrophages in the subsequent stages of wound healing is also decreased. However, it has been shown that these fetal neutrophils

and macrophages respond to appropriate signals *in vitro*. These data suggest that the attenuated inflammatory response is a result of decreased recruitment and not an intrinsic deficiency of the cells [20]. In addition, fetal platelets are shown to aggregate poorly and produce lower levels of profibrotic growth factors, such as TGF-β1 and platelet-derived growth factor (PDGF) [21]. Recent studies have demonstrated a paucity of mast cells in the fetal scarless phenotype. Mast cells in mid-gestation fetal wounds are less mature, decreased in number, and fail to degranulate in response to injury compared with scar forming wounds in late gestation [22].

Cytokines

The attenuated inflammatory response observed in fetal wound repair suggests that cytokines, which regulate inflammation, may have a characteristic profile associated with the scarless phenotype. Production of proinflammatory cytokines such as interleukin-6 (IL-6) and interleukin-8 (IL-8) are decreased in fetal skin compared with postnatal skin [23, 24]. Additionally, fetal fibroblasts stimulated by lipopolysaccharide or PDGF have an attenuated IL-6 and IL-8 response compared with adult fibroblasts [25]. This relative paucity of proinflammatory cytokines led to the investigation of the role of the anti-inflammatory cytokine interleukin-10 (IL-10) in fetal wound healing. IL-10 has been shown to deactivate macrophages and neutrophils, as well as diminishing the production of proinflammatory cytokines. Early gestation fetal skin, serum, and amniotic fluid express high levels of IL-10, whereas neonatal skin demonstrates minimal IL-10 expression [26]. Studies in mid-gestation fetal wounds created in transgenic IL-10 knockout mice have elevated levels of IL-6 and IL-8, and heal with a scar at a gestational age which normally heals scarlessly (Fig. 1) [27].

Most compellingly, independent laboratories have demonstrated that overexpression of IL-10 using viral vectors results in a dose-dependent recapitulation of fetal regenerative wound healing (Fig. 2) [25, 26]. This includes a decreased inflammatory cellular infiltrate, a characteristic fetal pattern of matrix deposition, a regeneration of dermal appendages, and overall wound healing that is indistinguishable from the surrounding skin. Wound repair in IL-10-treated postnatal incisional wounds occurred with restoration of normal skin integrity by biomechanical testing, which suggests that application of IL-10 may have benefits long after the vector and transgene are cleared from the wound[26]. These results suggest that an early expression of IL-10 initiates a cascade of events which results in the scarless wound healing phenotype. Further, these data support a cytokine hypothesis in which the shift toward increased anti-inflammatory cytokine expression relative to corresponding proinflammatory cytokine expression is permissive of the recapitulation of the fetal regenerative tissue repair.

These promising findings have led to the development of IL-10 as a potential therapeutic antiscarring agent, Prevascar, human recombinant IL-10. Following intradermal injection immediately preceding incision and an additional injection 24 h later, Prevascar was found to improve scar formation at 12 months in a randomized, double-blinded, placebo-controlled trial [28]. Further Prevascar trials are ongoing.

EXTRACELLULAR MATRIX

The characteristic type III collagen and hyaluronan-rich ECM are key components of the fetal scarless wound healing phenotype. This distinct ECM facilitates the migration of cellular components and also mediates the wound repair process via the interaction of cell-surface receptors.

Collagen

Both fetal and adult wounds heal with collagen deposition. In fetal wounds, collagen is deposited in a fine reticular pattern indistinguishable from the surrounding uninjured tissue. In postnatal wounds, collagen is deposited in densely arranged parallel bundles [29]. Although all wounds heal with predominantly type I collagen, there is a greater ratio of type III collagen to type I collagen deposited in fetal wounds compared with postnatal wounds. Type III collagen fibers are smaller compared with type I fibers and may allow a more reticular deposition of fibers in the wound [30, 31]. Also, type I collagen is found in more rigid tissues, whereas type III is found in more elastic tissue. This association with decreased amount of cross-linked collagen fibers may lead to a more flexible wound which may contribute to scarless repair. Additionally, in response to profibrotic growth factors such as TGF-β1, fetal fibroblasts have a characteristic response in collagen deposition compared with postnatal fibroblasts. This suggests fetal fibroblasts are programmed to form a more regenerative ECM [15].

Multiple efforts to minimize scarring have been made through the manipulation of collagen. Therapeutic efforts have been focused on inhibiting cross-linking in order to render the wound more susceptible to remodeling [32]. Unfortunately, these agents have been clinically ineffective thus far. There are, however, some reports of small molecular inhibitors of prolyl hydroxylase that may have therapeutic value but raise concern over skin integrity once healing is complete [33].

Hyaluronan

Fetal wounds have an increased level and prolonged elevation of high molecular weight (HMW) hyaluronan. Levels of HMW hyaluronan are increased in the fetus. Fetal tissues have increased levels for up to 3 weeks following injury, whereas in adult wounds hyaluronan levels are only transiently elevated and low molecular weight hyaluronan predominates [7, 34]. Hyaluronan also upregulates both TGF-β3 and type III collagen. Additionally, fetal fibroblasts have two-fold to four-fold greater hyaluronan-receptor expression, suggesting hyaluronan helps facilitate more rapid fibroblast migration [35]. Hyaluronan is also shown to suppress platelet aggregation and their release of growth factors in a dose-dependent fashion [36]. In a murine fetal organ culture model, the addition of hyaluronan to the late gestation wound resulted in the recapitulation of the scarless phenotype of mid-gestation [37]. In the past, hyaluronan has been considered to be a passive structural component; however, over the last decade it has been suggested that hyaluronan may have a significant role in wound healing by stimulating cell migration, differentiation, and proliferation in addition to its role as an integral component of the ECM [38].

Multiple applications of hyaluronan have been developed to minimize scarring. A hyaluronan-rich film, Seprafilm, has been developed to decrease intra-abdominal scarring and has been somewhat effective in decreasing intra-abdominal adhesions [39]. Topical applications of HMW hyaluronan have also been investigated with promising results [40].

BIOMECHANICAL FORCES

Not all mid-gestation fetal wounds heal without a scar. In contrast to small incisional wounds, larger excisional wounds heal with a characteristic scar at gestational ages that heal smaller wounds scarlessly. This suggests that biomechanical forces may be in part an underlying mechanism of the fetal regenerative phenotype [41]. A part of this explanation may come from the myofibroblast, a specialized cell that is known to produce profibrotic growth factors and promote rapid wound closure. The larger, scar-forming fetal wound may have increased shear forces and mechanical stress. Increased shear force results in mechanotransduction, which induces local production of profibrotic growth factors, such as TGF-β1 and TGF-β2 [42]. The mechanical stress induces the fibroblasts within the wound bed to differentiate into myofibroblasts, acquiring contractile properties through the expression of alpha-smooth muscle actin. Myofibroblasts are present in most fetal wounds, as early as day 1 following injury. In wounds that heal scarlessly, they are notably absent at day 14. In contrast, in wounds of the same gestational age that heal with a scar, myofibroblasts are present in abundance [41]. Further, mechanical forces affect scar formation through the regulation of cell–matrix interactions via intracellular focal adhesion components, such as focal adhesion kinase (FAK). In a recent study, FAK inhibition resulted in successful attenuation of inflammatory cell recruitment and decreased resulting scar formation [43▪].

The implications of decreasing transduction of profibrogenic mechanical stress are readily translated to postnatal wounds in the effort to minimalize scarring. A recent study demonstrated the value of offloading strain from the wound using a silicone mechanomodulating device applied to the peri-wound area, which resulted in significant decrease in fibrosis. Recent reports of phase I trials in patients using this strategy following abdominoplasty procedures have shown promise in ameliorating scar formation [44].

STEM CELLS

Multiple pluripotent stem cells have been proposed to play a role in fetal wound healing, including epithelial stem cells (ESCs), mesenchymal stem cells (MSCs), and ‘small dot’ cells. ESCs are interspersed throughout the basal layers. The slowly proliferating ESCs are surrounded by more quickly proliferating basal cells and their suprabasal progeny to form epidermal proliferative units. ESCs are also found within the bulge area of hair follicles. The stem cells within the bulge area migrate to the epidermis following injury and proceed to differentiate into dermal, vascular, and neural components [45]. MSCs have been shown to have a role in regenerative healing, including immunomodulation, anti-fibrosis, antiapoptosis, and angiogenesis [46▪▪]. Recent studies have shown MSCs to be a potent gatekeeper in preventing excessive inflammation. They have demonstrated the ability to immunoregulate through multiple independent pathways, including the induction of IL-10

secretion by macrophages [47▪]. Further evaluation of MSCs and scarless wound healing continues, with the need for more complete characterization of the cell population. ‘Small dot’ cells have also been identified to play a role in fetal wound healing. There is a 20-fold greater increase of these cells in fetal blood than postnatal blood. A recent study transplanting fluorescence-labeled ‘small dot’ cells in a postnatal murine incisional wound model showed migration of these cells to the wound bed with a decrease in scarring [48, 49▪▪]. Further study will help to elucidate the importance of these stem cell populations.

CONCLUSION

Wound healing is a complex process, requiring an orchestrated response of growth factors, cytokines, ECM components, modulation of biomechanical stress, and stem cells. The components in fetal regenerative healing are tightly regulated, favoring a pro-migratory, anti-inflammatory milieu in a characteristic ECM. The evidence suggests that there may be an early critical window in postnatal wound healing that may be amenable to manipulation to provide a permissive environment for scarless wound healing to proceed. The implications for scarless healing go far beyond cutaneous wound healing, with nearly every field of medicine affected by excessive scarring. Further research on the molecular mechanisms of fetal scarless wound healing has the potential to have therapeutic benefit for a wide array of diseases.

Acknowledgements

This study was supported in part by the grants from the National Institutes of Health (1K08GM098831) and the Wound Healing Society Foundation (SGK).

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KEY POINTS

- The fetal regenerative phenotype is characterized by a characteristic growth factor profile, anti-inflammatory response, extracellular matrix, and distinct biomechanical forces.
- Recent studies suggest an early critical window in postnatal wound healing that may be amenable to manipulation to provide a permissive environment for scarless wound healing to proceed.
- Further studies of pluripotent stem cells are needed to better understand their physiologic role and therapeutic potential.
- Understanding the underlying mechanism of fetal regenerative healing has the potential to lead to novel therapies to minimize scarring in any pathology characterized by excessive fibroplasia.

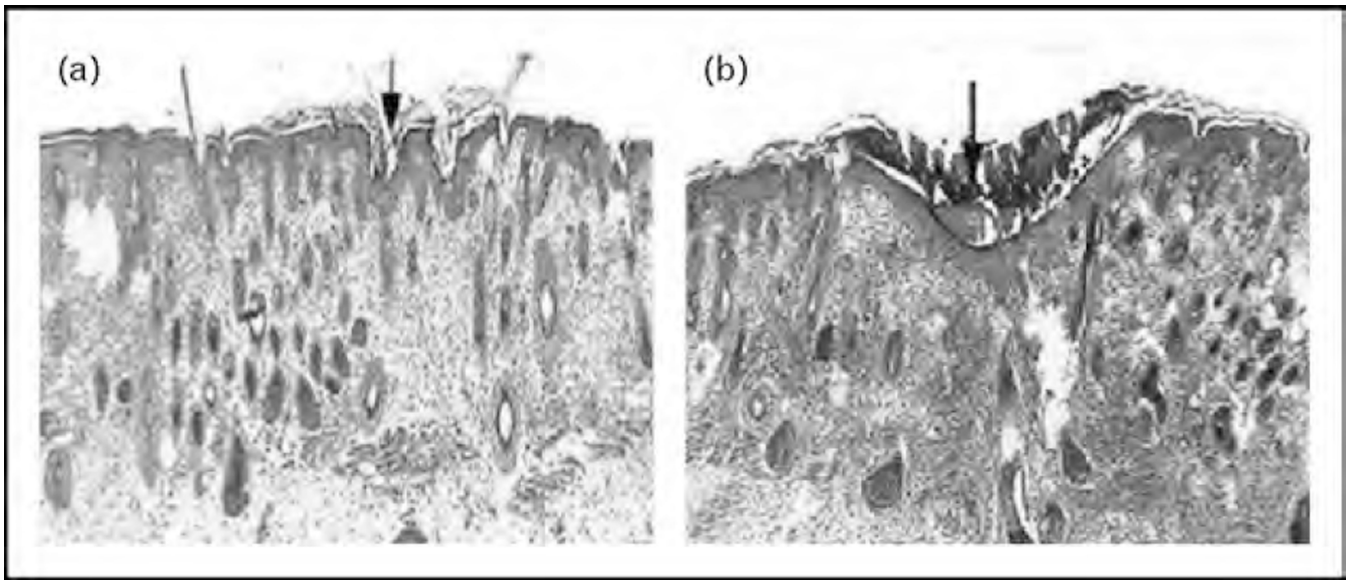

FIGURE 1.

Trichrome staining of normal (a) and IL-10 knockout (b) fetal mouse skin 7 days following incisional wound. Normal fetal skin results in minimal cellular infiltrate, normal distribution of dermal appendages, and reconstitution of reticular collagen deposition. In contrast, IL-10 knockout fetal mouse skin grafts from mice of the same gestational age demonstrate increased, dense collagen deposition (blue staining) with loss of dermal appendages consistent with scar formation. Site of incisional wound is indicated by the arrow. Data from [23]. IL-10, interleukin-10.

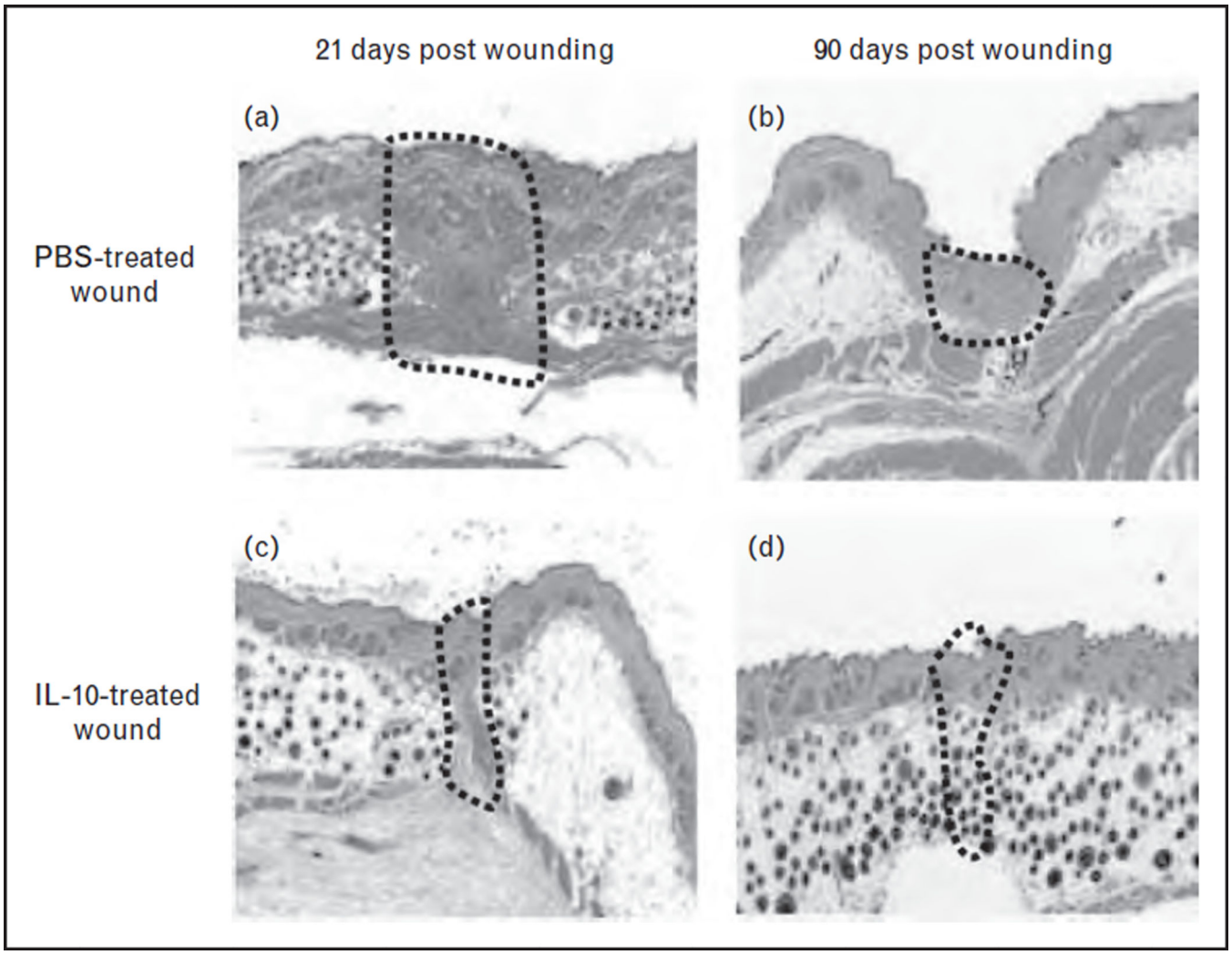

FIGURE 2.

Adenoviral-mediated overexpression of IL-10 results in minimal scar formation. At day 21, phosphate buffer solution (PBS)-treated skin shows a well-demarcated scar with dense, haphazardly arranged collagen fibers with a loss of dermal appendages (a). In contrast, in wounds treated with 1×10^9 plaque forming units Ad-IL-10, no well defined scar is seen, collagen is organized in a fine reticular pattern, and there is a normal distribution of dermal appendages (c). At day 90, the PBS-treated group shows a remodeled scar that is well organized and flattened with the dropout of dermal appendages (b). Ad-IL-10-treated wounds exhibit a reconstitution of a normal dermal reticular pattern of collagen deposition and dermal elements including hair follicles, with the wound being indistinguishable from surrounding unwounded skin (d, 5×).

Table 1

Comparison of fetal regenerative wound healing profile with postnatal wound healing

	Fetal	**Postnatal**
Phenotype	Regenerative	Scar formation
Growth factors		
bFGF	Lower	Higher
PDGF	Lower	Higher
VEGF	Higher	Lower
TGF-β		
TGF-β1	Low levels	High levels
TGF-β2	Low levels	High levels
TGF-β3	High levels	Low levels
Inflammatory response		
Inflammatory cell	Minimal	High levels leukocytes, macrophages, mast cells infiltrate
Cytokines		
Proinflammatory: IL-6, IL-8	Low levels	High levels
Anti-inflammatory: IL-10	High levels	Low levels
Extracellular matrix		
Collagen		
Histology	Fine, reticular weave	Thick, rope-like bundles
Type III collagen	High levels	Low levels
Deposition	Immediate	Delayed
Cross-linking	Low levels	High levels
TGF-β1-stimulated deposition	Absent	Present
Hyaluronan		
Expression	High levels	Low levels
	Persistent expression	Transient expression
Molecular weight	High	Low
HA receptors (fibroblast)	High levels	Low levels
Mechanical force		
Myofibroblast (day 14)	Absent	Present
Stem cells		
MSC	High levels	Lower levels
Dot cells	Present	Absent

bFGF, basic fibroblast growth factor; HA, hyaluronan; MSC, mesenchymal stem cell; PDGF, platelet-derived growth factor; TGF, transforming growth factor; VEGF, vascular endothelial growth factor.