Advances in wound care are of great importance in clinical injury management. In this respect, the nuclear receptor peroxisome proliferator-activated receptor (PPAR)β/δ occupies a unique position at the intersection of diverse inflammatory or anti-inflammatory signals that influence wound repair. This study shows how changes in PPARβ/δ expression have a profound effect on wound healing. Using two different in vivo models based on topical application of recombinant transforming growth factor (TGF)-β1 and ablation of the Smad3 gene, we show that prolonged expression and activity of PPARβ/δ accelerate wound closure. The results reveal a dual role of TGF-β1 as a chemoattractant of inflammatory cells and repressor of inflammation-induced PPARβ/δ expression. Also, they provide insight into the so far reported paradoxical effects of the application of exogenous TGF-β1 at wound sites.

Of the numerous cytokines produced at the wound site, TGF-β1 has the broadest effects, influencing nearly every aspect of tissue repair (1). TGF-β1 signals through a membrane receptor complex that recruits and phosphorylates Smad2 and 3 proteins. Once phosphorylated, they associate with Smad4 and translocate into the nucleus to control gene transcription in several ways (2, 3). Smad3-null mice, whose TGF-β1 signaling pathway is impaired, show accelerated wound healing characterized by enhanced reepithelialization, increased keratinocyte proliferation, and reduced immune cell infiltration (4). Interestingly, TGF-β1-null mice display either delayed or accelerated wound healing depending on the model analyzed (5, 6). Equally complex is the effect of exogenous TGF-β1 on a wound because the healing rate was found to be dependent on the delivery vehicle, dose of the growth factor, its application schedule, and wound model (7–9). In a rabbit ear dermal ulcer model, a single application of TGF-β1 at the time of wounding had a beneficial effect equal to that of multiple doses, whereas application 24 h after wounding did not improve healing (10).

Doses of TGF-β1 used to treat wounds topically have varied over a 1,000-fold concentration range from a few ng to several μg, depending on delivery vehicle and wound models (8, 9, 11, 12). All studies have shown a bell-shaped dose-dependent response to TGF-β1, with either no or decreasing effects at lower or higher than optimal concentrations. The reason for such diverse responses to exogenous TGF-β1 is part of the present investigation.

The nuclear receptor PPARβ/δ plays critical roles in the keratinocyte response to inflammation signals produced immediately after a skin injury. Its inflammation-induced increase in activity at the wound edge maintains a sufficient number of viable keratinocytes for reepithelialization (13–15). Using exogenous TGF-β1 application as well as Smad3 and PPARβ/δ single- and double-knock-out mice, we provide evidence for an in vivo cross-talk between TGF-β1 and PPARβ/δ signaling.

**Experimental Procedures**

**Reagents—**Anti-ILK, anti-PDK1, and anti-Mac3 were from Santa Cruz Biotechnology, Inc. Anti-Akt1(also known as protein kinase B alpha), anti-phospho-Akt-Thr308, anti-phospho-Akt-Ser473, and an in vitro Akt kinase assay kit were from Cell Signaling. Anti-keratin 6 (K6), anti-filaggrin, anti-involucrin, and anti-Ki67 were from Babco. Anti-PPARγ was from Affinity Bioreagent. Anti-α-smooth muscle actin (α-SMA) and anti-α-SMA-fluorescein isothiocyanate were from Sigma. Recombinant TGF-β1 was from PeproTech EC. The specificity of the anti-PPARγ antibody was verified as shown in Fig. S4.

**Animals and Wounding Experiments—**PPARβ/δ−/− Smad3−/− mice were obtained by breeding male Smad3−/− with female PPARβ/δ−/− mice. Smad3−/− and PPARβ/δ−/− Smad3−/− mice were obtained by interbreeding PPARβ/δ−/− Smad3−/− littersmates. Females and males homozygous for the Smad3 deletion are sterile and hypotertile, respectively. Hence, Smad3−/− littersmates were intercrossed to obtain the wild type, Smad3+/−, and Smad3−/− mice, whereas the PPARβ/δ−/−, PPARβ/δ−/− Smad3−/−, and PPARβ/δ−/− Smad3−/− mice were obtained by PPARβ/δ−/− Smad3−/− breeding. All mice used in this study are in C57BL/6 background and were individually caged, housed in a temperature-controlled room (23 °C) on a 10 h dark/14 h light cycle, and fed with the standard mouse chow diet.

Wounding and healing analyses were performed on 6-week-old females as described previously (6, 14). Briefly, the hair follicle cycle of each mouse was synchronized by shaving the back of the animal 2 weeks before starting the experiment. Mice were then anesthetized, shaved, and a full thickness middorsal wound (0.5 cm², square-shaped) was created by excising the skin and the underlying panniculus carnosus. Wound closure was measured daily in a double-blinded fashion until complete wound closure. A subset of wild type animals was treated topically with either vehicle (3% methylcellulose in phosphate-buffered saline and 4 mM HCl) or 100 ng of TGF-β1. Treatments were rotated to avoid site bias. At the indicated days postwounding, the entire wound was excised, the area of injury measured, and the wound closure calculated.

This paper is available on line at http://www.jbc.org
The pleiotropic effects of exogenous TGF-β1 on wound closure depend on numerous factors (1). Recently, we discovered a cross-talk between PPARβ/δ and TGF-β1/Smad3 signaling in primary keratinocytes (16), but the effects of exogenous TGF-β1 at injury site, in vivo, were not investigated. Here, we studied these effects on PPARβ/δ expression and wound closure. Recombinant TGF-β1 was applied either immediately upon (TGF-β1(day 0)) or 2 days after injury (TGF-β1(day 2)).

**RESULTS**

**Time-dependent Effect of Exogenous TGF-β1 on Wound Healing**

The pleiotropic effects of exogenous TGF-β1 on wound closure and takes place when the granulation tissue is populated with myofibroblasts. Because TGF-β1 is a major cytokine of myofibroblast differentiation (17), we next examined the presence of these cells in wound biopsies using α-SMA as a specific marker. Consistent with other reports, the expression of α-SMA peaked between days 7 and 10 after injury (Figs. 1B and S2A) (18, 19). In TGF-β1(day 0)-treated wounds, a higher expression of α-SMA was already detected at day 5. Subse-

**TGF-β1(Day 0) Treatment**—The TGF-β1(day 0) treatment accelerated wound repair with a complete closure at days 13–14 compared with the vehicle-treated wounds, which closed at day 17 (Figs. 1A and S1A). Wound biopsy analyses showed that the expression of PPARβ/δ was already elevated 24 h after application, an accelerated response compared with vehicle-treated wounds (Figs. 1B and S2A). Although PPARβ/δ levels did not reach the peak observed in vehicle-treated wounds, they remained elevated for up to 5 days after injury. As expected, the expression patterns of two PPARβ/δ target genes, ILK and PDK1, and hence Akt1 activity, were changed according to the altered PPARβ/δ expression profile (Figs. 1B and S2A) (13).

Wound contraction also contributes to wound closure and takes place when the granulation tissue is populated with myofibroblasts. Because TGF-β1 is a major cytokine of myofibroblast differentiation (17), we next examined the presence of these cells in wound biopsies using α-SMA as a specific marker. Consistent with other reports, the expression of α-SMA peaked between days 7 and 10 after injury (Figs. 1B and S2A) (18, 19). In TGF-β1(day 0)-treated wounds, a higher expression of α-SMA was already detected at day 5. Subse-
independent experiments.

Indeed, 24 h post-treatment, a higher number of Mac3-positive macrophages infiltrated the TGF-β1 wound biopsies (Figs. 1C, S2B) versus vehicle, indicating that the optimal range was surpassed rapidly. The inability to summon further recruitment of macrophages resulted in TGF-β1 repression of PPARβ/δ expression.

We performed immunohistochemistry on wound biopsies sampled 24 h after the treatment. Consistent with the higher levels of PPARβ/δ mRNA expression (Fig. 1B), more PPARβ/δ-positive keratinocytes were detected in TGF-β1 (day 2)- and vehicle-treated biopsies (TGF-β1 versus vehicle, 94.6 ± 7.5 versus 36.5 ± 3.2% section) (Fig. 1C). Because TGF-β1 is one of the most potent chemoattractants for macrophages and neutrophils at the injury site (20), we suspected that an early recruitment of a higher number of inflammatory cells would accelerate the release of cytokines, such as tumor necrosis factor-α, which up-regulate PPARβ/δ expression and activity (15, 21). Indeed, 24 h post-treatment, a higher number of Mac3-positive macrophages infiltrated the TGF-β1 (day 0)-treated compared with vehicle-treated control wounds (TGF-β1 versus vehicle, 109.6 ± 15.2 versus 34.2 ± 7.7% section) (Fig. 1C).

We propose that these early recruited macrophages produce enough inflammatory cytokines to overcome the inhibitory action of TGF-β1 on PPARβ/δ (16) and to up-regulate its expression. Indeed, the chemotactic dose response to TGF-β1 follows a bell-shaped curve (2). Consistent with other reports showing that the infiltration of macrophages begins 48 h postinjury (22, 23), the optimal response occurs around days 2–4 in the vehicle-treated mice, when the expression of PPARβ/δ is high and that of α-SMA low (Fig. 1D). In TGF-β1 (day 0)-treated wound, the infiltration of macrophages occurs earlier, between days 1 and 2 (Fig. 1D), producing a sufficient amount of cytokines to overcome the inhibitory action of TGF-β1 on PPARβ/δ. Accordingly, a different outcome with a later application of the TGF-β1 treatment is expected.

**TGF-β1 (Day 2) Treatment**—A later exposure to TGF-β1, 48 h after injury (TGF-β1 (day 2) treatment), resulted in a significant, but transient delay in reepithelialization, with a wound closure time similar to that of the vehicle-treated wound (Figs. 2A and S1B). Interestingly, the peak of increased PPARβ/δ expression typically observed in vehicle-treated wound biopsies was strongly repressed by the TGF-β1 (day 2) treatment (Figs. 2B and S2B). The diminished PPARβ/δ expression also resulted in reduced ILK and PDK1 expression as well as reduced Akt1 activity (Figs. 2B and S2B). In contrast, an early increase in α-SMA expression was detected already at day 3 and peaked between days 5 and 10 (Figs. 2B, S2B, and S3).

Immunohistochemistry of day 3 postwound biopsies, i.e., 24 h after TGF-β1 treatment, revealed fewer PPARβ/δ-positive keratinocytes (TGF-β1 versus vehicle, 25.6 ± 3.4 versus 86.6 ± 2.5% section). In contrast to TGF-β1 (day 0) treatment, there was no difference in the amount of infiltrating macrophages between vehicle-treated and TGF-β1 (day 2)-treated samples (Fig. 2C). The TGF-β1 (day 2) treatment also shifted the chemotactic
response to an earlier time point (Fig. 2D). But in contrast to the TGF-β1(day 0) treatment, we speculate that this delayed administration of TGF-β1, added to already high endogenous TGF-β1, exceeds the optimal TGF-β1 dose for chemotaxis. Consequently, no further increase in infiltrating inflammatory cells was observed (Fig. 2C), and thus the TGF-β1 repression on inflammation-stimulated expression of PPARβ/δ was not overcome (16).

To gain further insights into the dual effect of exogenous TGF-β1, similar experiments were performed on Smad3-null mice. Regardless of the application schedule, TGF-β1(day 0) or TGF-β1(day 2), no significant increase in the number of Mac3-positive macrophages was detected in 24-h post-treatment biopsies compared with vehicle-treated wounds (Fig. S5). This suggests that Smad3 is critical for TGF-β1-mediated chemotaxis, which is consistent with earlier reports showing that topical applications of TGF-β1 immediately before wounding did not influence inflammatory cell recruitment in Smad3-deficient mice (4, 24).

Taken together, these results underscore a finely tuned temporal balance between inflammatory signals and TGF-β1 in the regulation of PPARβ/δ expression and hence of wound repair. They also suggest that prolonged PPARβ/δ expression promotes rapid wound closure.

To understand better the effect of TGF-β1 on the PPARβ/δ expression profile, we examined full thickness excisional wound repair using Smad3−/− mice. As reported earlier (5), we also observed an accelerated wound closure rate in the Smad3−/− mice compared with their wild type (WT) littermates (Fig. 3A; Smad3−/− versus WT; closure completed at day 10 versus 17, respectively). Wound biopsies from the WT mice showed a peak of PPARβ/δ mRNA expression 3 days postinjury. Interestingly, in Smad3 mutant mice (Smad3−/− and Smad3+/−), a premature maximal increase in PPARβ/δ expression was already detected 24 h postwounding, which remained high throughout the following 6 days (Figs. 3B and S6A). This sustained PPARβ/δ expression resulted in similar prolonged expression levels of ILK and PDK1 (Figs. 3B, and S6, A and B) and, consequently of Akt1 kinase activity (Figs. 3C and S6B). These results emphasize the role of Smad3 in mediating the down-regulation of inflammation-induced PPARβ/δ by TGF-β1. Very interestingly, these profiles are reminiscent of those observed after TGF-β1(day 0) treatment (see Fig. 1B).

To evaluate the effect of the prolonged PPARβ/δ expression on reepithelialization, we performed immunohistochemistry on

**FIG. 3.** Prolonged PPARβ/δ expression is associated with accelerated wound healing in Smad3 mutant mice. A, wound closure kinetics of WT and Smad3−/− mice. Surface areas are plotted as a percentage of day 0 (= 100%) wound surface area (± S.E., n = 24). Arrows indicate the mean time for complete wound closure. Quantification of relative levels of PPARβ/δ, ILK, and PDK1 mRNA, (B) and ILK, PDK1 protein expression, and Akt1 activity levels (C) in wound biopsies from WT and Smad3−/− mice are shown (see also Fig. S6). Akt1, Akt1-threonine 308, and Akt1-serine 473 protein levels are shown in Fig. S6B. Graphs show the mean -fold changes in PPARβ/δ, ILK, PDK1 mRNA, protein, and Akt1 activity levels from at least six (>12 wounds) independent experiments.
section; Fig. S4), and more phosphorylated Akt1 was detected in parallel, the number of apoptotic abundant (Fig. 4B), a region where phosphorylated Akt1 was more thelium (Smad33/−) keratinocytes was detected in the lower layers of the neoepi-

A

B

Fig. 4. Immunohistochemical analyses of day 5 wound biopsies from WT and Smad33/− mice. A, representative pictures of K6-immunostained skin wound sections from WT and Smad33/− mice 5 days postinjury. Black arrows indicate the wound edge. B, phosphorylated Akt1-serine 473, Akt1-threonine 308, PPARβ/δ, Ki67 antibodies (for proliferation), and TUNEL assay (for apoptosis) are presented. The different panels show a representative field of labeling obtained at the wound region. Red arrows, intense immunostaining of Akt1-threonine 308 at leading wound edges. White dotted line, wound epidermis-dermis interface. The mean numbers of TUNEL-, Ki67-, and PPARβ/δ-positive cells (representatives indicated by white arrows) were counted from six wound sections (K6-positive regions, excluding hair follicles), performed on five different animals for each genotype. c, clot; hf, hair follicle.

wound biopsies at day 5, when the expression levels of PPARβ/δ, PDK1, ILK, and the activity of Akt1 were dramatically higher in Smad33/− wounds. Compared with WT mice, Smad33/− mice exhibited a thicker hyperproliferative and more extended epithelial tongue at the wound site, as revealed by K6 staining (Fig. 4A). Consistent with the sustained PPARβ/δ mRNA and Akt1 activity levels, a higher number of PPARβ/δ-positive keratinocytes was detected in Smad33/− biopsies (WT versus Smad33/−, 32.4 ± 3.1 versus 68.4 ± 2.1/section; Fig. S4), and more phosphorylated Akt1 was detected at the leading wound edges and in the basal wound keratinocytes (Fig. 4B).

Both PPARβ/δ and Smad3 play critical roles in the balance between keratinocyte proliferation and apoptosis (15, 16). In Smad33/− mice, a higher number of proliferating Ki67-positive keratinocytes was detected in the lower layers of the neoeplithelium (Smad33/− versus WT, 209.8 ± 4.6 versus 77.8 ± 2.3/section), a region where phosphorylated Akt1 was more abundant (Fig. 4B). In parallel, the number of apoptotic TUNEL-positive cells that are restricted to the upper layers was reduced in Smad33/− wound biopsies compared with their WT littermates (Fig. 4B; Smad33/− versus WT, 11.2 ± 1.3 versus 36.1 ± 4.9/section).

Together, these results provide evidence for prolonged epidermal PPARβ/δ expression in Smad33/− mice, which produces a prolonged Akt1 activity, higher keratinocyte proliferation, and lower apoptosis rates in the regenerating epithelium. Most importantly, these events are associated with much faster healing in Smad33/− mice.

Sustained PPARβ/δ Expression and Activity Are Required for Rapid Wound Closure

To demonstrate further that the prolonged PPARβ/δ expression is responsible for the accelerated wound closure in the Smad3 mutant mice, we examined wound healing in PPARβ/δ and Smad3 double-knock-out animals (PPARβ/δ−/−Smad3−/−), which were growth retarded (Table I). Similar growth retardation was seen in PPARβ/δ−/− and Smad3−/− single-null animals albeit with reduced severity. Consistent with the role of PPARβ/δ in hair follicle development (25) and keratinocyte differentiation (21), the PPARβ/δ−/−Smad3−/− animals also showed a transient delay in neonatal hair growth (Fig. 5A) as well as altered filaggrin and involucrin expression as revealed by immunofluorescence (Fig. 5B). However, between weeks 6 and 9, at the time of the wound experiments, no apparent aberrant skin phenotype was observed. ILK/PDK1 expression and Akt1 activity were similar in PPARβ/δ−/− and PPARβ/δ−/−Smad3−/− wound biopsies (Fig. 6A). However, compared with the WT and Smad3−/− biopsies, both ILK/PDK expression and Akt1 activity were reduced (Figs. 3B, 6A, and 6C). Although TGF-β1 has been implicated in phosphoinositide 3-kinase/Akt1 signaling in other cell types (26, 27), our results clearly underscore a prominent role of PPARβ/δ in modulating Akt1 activity during skin wound healing.

In the PPARβ/δ-deficient day 5 wound biopsies, a 15–20-fold increase in the number of apoptotic keratinocytes was observed (PPARβ/δ−/− versus WT, 391.1 ± 10.2 versus 36.1 ± 4.9/section; PPARβ/δ−/−Smad3−/− versus Smad3−/−, 424.5 ± 8.6 versus 21.5 ± 2.2/section). Furthermore, in contrast to WT and Smad3−/− biopsies, apoptotic keratinocytes were detected throughout the entire wound epidermis in the PPARβ/δ-deficient mice (Figs. 4B and 6B). This dramatic increase in apoptotic keratinocytes, as a result of PPARβ/δ deficiency, significantly delayed wound closure by 7–14 days compared with Smad3−/− and WT mice (Figs. 3A and 6C). Both PPARβ/δ−/− and PPARβ/δ−/−Smad3−/− mice had a lower number of proliferating keratinocytes than the WT mice (WT, PPARβ/δ−/−, and PPARβ/δ−/−Smad3−/−: 74.3 ± 6.8, 53.0 ± 6.1, and 43.9 ± 3.8/section, respectively), which further delayed wound closure in these animals (Figs. 4B and 6B).

These results reveal that in vivo PPARβ/δ and Smad3 coordinate the balance between keratinocyte apoptosis and proliferation. Importantly again, a prolonged elevated PPARβ/δ expression profile favors a rapid wound closure.

DISCUSSION

Efficient wound repair after an injury is crucial to the survival of any organism. The results herein demonstrate that, either via external conditioning of the wound site by topical application of TGF-β1 or genetic ablation of the Smad3 gene, a prolonged elevated expression and activity of PPARβ/δ dictates an accelerated wound closure. This prolonged PPARβ/δ activity allows for extended Akt1 activity that reduces apoptosis and increases proliferation of keratinocytes at the wound site, and hence promotes faster healing.

The differential effects of exogenous TGF-β1 on wound closure underscore the complexity of the wound repair mechanism. The TGF-β1 (day 0) treatment accelerates, whereas the
TGF-β1 (day 2) application transiently delays wound healing. The balance between promotion and slowdown of healing depends on doses and the application schedule of TGF-β1. Analyses of these parameters suggest that the described paradoxical actions of exogenous TGF-β1 on wound healing most likely reside in its dual role. As a chemoattractant of immune cells, it stimulates PPARβ/δ expression via the production of inflammatory cytokines (28). As a repressor, it reduces the inflammatory cytokines that up-regulate PPARβ/δ expression (15). In the Smad3−/− mice, despite the impaired local inflammatory response (4), the enhanced and sustained expression of PPARβ/δ results from a loss of the suppressive effect of Smad3 on the expression of PPARβ/δ (17).

In the TGF-β1 (day 2) protocol, despite the strong suppression of inflammation-induced PPARβ/δ expression and a transient healing delay, a similar time point of complete wound closure was observed compared with vehicle-treated mice. This apparent discrepancy with our earlier reports describing a delayed wound closure in PPARβ/δ-deficient mice (14, 28) is most likely for two reasons. First, the TGF-β1 (day 0) protocol, the chemoattractant effect of exogenous TGF-β1 triggers an early infiltration of immune cells, which produce inflammatory cytokines that up-regulate PPARβ/δ expression (15). In the Smad3−/− mice, despite an impaired local inflammatory response (4), the enhanced and sustained expression of PPARβ/δ results from a loss of the suppressive effect of Smad3 on the expression of PPARβ/δ (17).

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At first sight, it may appear difficult to reconcile the observations between those obtained from Smad3−/− mice and TGF-β1 (day 0)-treated animals. Notably, the TGF-β1 (day 0) treatment influenced the PPARβ/δ expression profile such that it was almost identical to that of Smad3 mutant mice, which explains the similarities of the healing kinetics. Despite a similar outcome, the means by which it is reached in the two different experimental models are different. In the TGF-β1 (day 0) protocol, the chemoattractant effect of exogenous TGF-β1 triggers an early infiltration of immune cells, which produce inflammatory cytokines that up-regulate PPARβ/δ expression (15). In the Smad3−/− mice, despite an impaired local inflammatory response (4), the enhanced and sustained expression of PPARβ/δ results from a loss of the suppressive effect of Smad3 on the expression of PPARβ/δ (17).

Fig. 5. Skin abnormalities in PPARβ/δ and Smad3 mutant mice. A, dorsal (left) and ventral (right) view of a 1-week-old WT (PPARβ/δ+/+; Smad3+/+) and a double-knock-out (PPARβ/δ−/−; Smad3−/−; DKO) pup. Double-knock-out pups showed growth retardation and transient delay in neonatal hair growth, which is most visible on the ventral side. B, altered expression of epidermal differentiation markers in 6-week-old PPARβ/δ−/−; Smad3−/− mice as revealed by immunofluorescence staining of filaggrin and involucrin (green). DAPI (blue) was used to counterstain nuclei. The epidermis–dermis interface is indicated by the white dotted line. HE, hematoxylin-eosin; hf, hair follicle.

Table 1

| No. | Average weight | 4 weeks | 6 weeks | 8 weeks |
|-----|----------------|---------|---------|---------|
| WT  | 17.83 ± 0.51   | 22.21 ± 0.93 | 25.67 ± 0.57 |
| PPARβ/δ−/− | 15 | 14.82 ± 0.41 | 16.89 ± 0.63 | 19.60 ± 1.70** |
| Smad3+/+ | 15 | 18.17 ± 0.67 | 20.86 ± 0.78 | 26.17 ± 0.68 |
| Smad3−/− | 15 | 14.21 ± 0.48 | 18.52 ± 0.75 | 22.81 ± 0.63* |
| PPARβ/δ−/−; Smad3+/+ | 15 | 13.66 ± 0.79 | 17.82 ± 0.48 | 20.29 ± 1.30 |
| PPARβ/δ−/−; Smad3−/− | 15 | 10.34 ± 0.22 | 12.11 ± 0.43 | 15.16 ± 0.72** |

Values were subjected to the Mann-Whitney test compared with WT (*, p < 0.05 and **, p < 0.01).
shown recently that α-SMA expression is antagonistically regulated by TGF-β1 and interleukin-1. The latter is present abundantly during the early inflammation phase of wound repair (29). Of interest is the inverse expression pattern between PPARβ/δ and Akt1 activity on the one hand and α-SMA expression on the other hand. This is consistent with earlier studies (3, 16, 30, 31), which showed that elevated phosphorylated Akt may inhibit the transcriptional activity of Smad3, which is crucial to the up-regulation of α-SMA expression (17, 32).

For PPARβ/δ ligands to be considered as potential wound repair drugs, several factors including application schedule, bioavailability, and dose have to be taken into account. The narrow peak of increase in PPARβ/δ expression after injury corresponds to a small time window for effective ligand activation of the receptor. A timely biochemically controlled attenuation of TGF-β1/Smad3 signaling, which leads to a prolonged PPARβ/δ expression and also reduces fibrotic tissue (4, 33), coupled with an increase in PPARβ/δ activity by an agonist, should result in an accelerated rate of wound repair with minimal scarring.

Our results suggest that monitoring changes in the PPARβ/δ expression profile may serve as a very useful indicator of the differential effects of exogenous TGF-β1 or alternative treatments on wound closure. Such insights into how incoming extracellular signals regulate PPARβ/δ, which in turn coordinates their action on wound healing, may aid in the development of better treatments for ulcers and chronic wound disorders.

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