Functions of the Peroxisome Proliferator-Activated Receptor (PPAR) α and β in Skin Homeostasis, Epithelial Repair, and Morphogenesis

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The three peroxisome proliferator-activated receptors (PPARα, PPARβ, and PPARγ) are ligand-activated transcription factors belonging to the nuclear hormone receptor superfamily. They are regarded as being sensors of physiological levels of fatty acids and fatty acid derivatives. In the adult mouse skin, they are found in hair follicle keratinocytes but not in interfollicular epidermis keratinocytes. Skin injury stimulates the expression of PPARα and PPARβ at the site of the wound. Here, we review the spatiotemporal program that triggers PPARβ expression immediately after an injury, and then gradually represses it during epithelial repair. The opposing effects of the tumor necrosis factor-α and transforming growth factor-β-1 signalling pathways on the activity of the PPARβ promoter are the key elements of this regulation. We then compare the involvement of PPARβ in the skin in response to an injury and during hair morphogenesis, and underscore the similarity of its action on cell survival in both situations.

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INTRODUCTION

The peroxisome proliferator-activated receptor α (PPARα) was identified in the early 1990s as the target of compounds that cause proliferation of peroxisomes in rodent liver (Issemann and Green, 1990). Three PPAR isotypes were then identified in rodents, frogs, fishes, and humans, named PPARα (NR1C1), PPARβ/δ (NR1C2, called PPARβ herein) and PPARγ (NR1C3) (Desvergne and Wahli, 1999). They are ligand-induced transcription factors belonging to the nuclear hormone receptor superfamily that also includes, amongst others, retinoid X receptors, the vitamin D receptor, thyroid hormone receptors, and estrogen receptors.

PPARs are considered to be sensors, especially for polyunsaturated fatty acids and diverse fatty acid derivatives (Forman *et al.*, 1997; Kliewer *et al.*, 1997; Krey *et al.*, 1997). Polyunsaturated fatty acids like arachidonic acid or linoleic acid are potent activators of the three PPARs. Arachidonic acid derivatives such as leukotrienes and prostaglandins are PPAR agonists that show higher selectivity towards PPARα, PPARβ, and PPARγ, respectively (Kersten and Wahli, 2000). In addition, several synthetic marketed drugs are PPAR ligands, such as the fibrates used to treat dyslipidemia through PPARα activation, and the antidiabetic thiazolidinediones that activate PPARγ.

From a structural point of view, PPARs display the characteristic organization of nuclear receptors. The N-terminal A/B domain containing a putative ligand independent transactivation function (AF-1) is flanked by the C-domain which binds DNA via a two zinc finger motif. The C-domain is linked by a short hinge domain (D) to the C-terminal ligand-binding domain, also called the E/F domain, which contains the ligand-dependent transactivation function AF-2. In the PPARα and γ isotypes, the ligand-independent transactivation function can be regulated by phosphorylation via activation of the mitogen-activated protein kinase pathway (Diradourian *et al.*, 2005; Gelman *et al.*, 2005). Upon fixation of an agonist, a conformational change in the structure of the ligand-binding domain creates the interface required for interactions with coactivators, such as SRC-1 or CBP/p300, which results in the transactivation of target genes. Alternatively, PPARs can exert transrepression of gene activity via mechanisms that were reviewed recently (Feige *et al.*, 2006).

Mainly expressed in the liver and brown adipose tissue, but also found at lower levels in the gut, muscle, and kidney, PPARα is involved in lipid catabolism (Kersten *et al.*, 2000) and exerts anti-inflammatory effects (Delerive *et al.*, 2001; Genolet *et al.*, 2004; Kostadinova *et al.*, 2005). Interestingly, PPARα is also expressed in the epidermis following a skin

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Abbreviations: COX-2, cyclooxygenase-2; PPAR, peroxisome proliferator-activated receptor; TNF-α, tumor necrosis factor-α; TGF-β, transforming growth factor-β

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injury, as will be discussed below (Michalik *et al.*, 2001). PPARγ is involved in adipocyte differentiation and lipid storage, as well as in the control of inflammatory reactions. It is mostly expressed in adipose tissue, gut, and the immune system and is induced in the liver by a high-fat diet (Kersten *et al.*, 2000). PPARβ, which has remained the less understood isotype, displays an ubiquitous expression often at levels that are higher than those of the two other isotypes (Escher *et al.*, 2001). Its upregulation in the murine interfollicular epidermis is of particular importance during skin wound healing (Michalik *et al.*, 2001; Tan *et al.*, 2001).

PPAR EXPRESSION IN HEALTHY AND INJURED SKIN

Single cell metabolism as well as intercellular interactions depend on complex mechanisms that ensure cell and tissue maintenance and renewal in a highly coordinated manner. The skin is a barrier against various environmental aggressions and dehydration, and is prone to be wounded. Following an injury and the inflammatory response it induces, repair is a survival process that involves activation of cells and their interactions with the extracellular matrix (ECM) to restore the integrity of the wounded area (Midwood *et al.*, 2004). This repair is a life-saving priority process initiated by the disruption of the blood vessels that in turn triggers platelet activation and release of cytokines and growth factors. Immune cells invade the newly formed blood clot, and become involved in cell debris phagocytosis and the secretion of many inflammatory cytokines (Werner and Grose, 2003). This initial inflammatory stage is followed by the proliferative and migratory phases of the repair process. The proliferation of activated keratinocytes and their migration following directional sensing contribute to the re-epithelialization of the wound. In parallel, dermal repair involves recruitment and proliferation of fibroblasts – which produce extracellular matrix—and angiogenesis—which provides blood supply to the newly regenerated tissue. Fibroblasts also secrete growth factors stimulating re-epithelialization (Birch *et al.*, 2005). Their differentiation into myofibroblasts allows wound contraction and tissue remodelling, the last steps in the wound-repair process (Desmouliere *et al.*, 2005).

PPARα and PPARβ expression is upregulated during the repair process, whereas PPARγ remains undetectable in the wounded murine interfollicular epidermis. The upregulation of PPARα is transient and correlates with the inflammatory phase, while that of PPARβ lasts over the entire healing process. The absence of PPARα in PPARα-null mice results in only a transient delay in wound repair, whereas completion of wound closure in animals lacking PPARβ is retarded for 2–3 days (Michalik *et al.*, 2001).

PPARα AND PPARβ ARE IMPORTANT PLAYERS IN THE KERATINOCYTE RESPONSE TO SKIN INJURY

As mentioned above, the kinetics of wound closure in PPARα null mice reveal no overall delay in healing. However, during the first 4 days following an injury a transient delay coinciding with the inflammatory phase is observed, but later on normal wound-healing efficiency is restored. Monitoring inflammatory cell infiltration revealed an impaired recruitment of neutrophils and monocytes/macrophages to the wound bed in PPAR$\alpha^{-/-}$ animals (Michalik *et al.*, 2001). Transgenic mice expressing a dominant-negative form of PPARα in the epidermis (PPAR$\alpha\Delta$13) were used to determine whether this observation is the consequence of the genetic ablation of PPARα in immune cells and fibroblasts, or arises from a defect in keratinocytes. Interestingly, the PPAR$\alpha\Delta$13 mice displayed the same pattern in wound closure as the PPAR$\alpha^{-/-}$ mice, with a transient delay in repair overlapping with the inflammatory phase (Michalik *et al.*, 2005). No defect in immune cell recruitment was observed in these mice. However, an increase in the expression of tumor necrosis factor (TNF)-α indicated that the inflammatory reaction is exacerbated in PPAR$\alpha\Delta$13-wounded skin. This revealed a loss of control of the inflammatory process in the transgenic animals.

The upregulation of PPARβ expression in wound healing is correlated to keratinocyte proliferation, adhesion, and migration upon the extracellular matrix in order to re-epithelialize the wounded region. Consistent with this, the delay observed in wound repair of PPAR$\beta^{+/-}$ mice overlaps with these healing phases. The key molecular processes responsible for PPARβ upregulation in keratinocytes were elucidated using primary keratinocyte cultures and a conditioned medium to mimic the inflammatory phase of wound repair (Tan *et al.*, 2001). Following the release of pro-inflammatory cytokines such as TNF-α, the stress-associated protein kinase pathway is activated, leading to the stimulation of PPARβ expression through AP-1 binding to its promoter. In parallel, activation of the primary keratinocytes by pro-inflammatory cytokines triggers the production of an endogenous ligand for PPARβ (Tan *et al.*, 2001). PPARβ then plays the role of a key transcription factor relaying inflammatory signals into cellular responses such as inflammation-induced differentiation, control of proliferation and resistance to apoptosis in keratinocytes. In the wound-healing process, PPARβ promotes cell survival through a direct activation of the genes coding for integrin-linked kinase and 3-phosphoinositide-dependent kinase-1, and consequent activation of the PKBα/Akt1 kinase (Di-Poi *et al.*, 2002). In addition, PPARβ is implicated in cell adhesion and migration as reflected by defects seen in the primary keratinocyte cultures (Tan *et al.*, 2001).

Using an apoptotic-derived conditioned medium that mimics the late re-epithelialization or remodelling stages of wound healing, we have identified transforming growth factor (TGF)-β1 as the cytokine that antagonizes TNF-α-induced PPARβ expression in keratinocytes (Tan *et al.*, 2004). This inhibitory effect occurs through the interaction of c-JUN with Smad3 (a downstream effector of TGF-β1 signalling), preventing the binding of c-JUN-p300 to the AP-1 site in the PPARβ promoter. Interestingly, both TNF-α induction of PPARβ expression, and its downregulation by TGF-β1 converge on the same AP-1 response element, either bound by or depleted of c-jun. A prolonged expression of PPARβ obtained through genetic ablation of Smad3 (Smad3$^{-/-}$) (Ashcroft *et al.*, 1999), or through early treatment with

TGF-β1 (day 0) accelerates skin wound closure (Tan *et al.*, 2005) (Figure 1). In agreement with the sustained expression of PPARβ during wound closure, a prolonged increase of PKBα/Akt1 activity was also observed in these conditions. According to the role of TGF-β1 as a chemo-attractant for macrophages and neutrophils (Wahl *et al.*, 1987), an increase in the number of recruited macrophages into the wound bed was observed in the animals treated with TGF-β1 on the day of injury, compared to vehicle-treated animals (Tan *et al.*, 2005). Therefore, we propose that early recruited macrophages produce a sufficient amount of inflammatory cytokines to overcome the inhibitory effect of TGF-β1 on PPARβ expression, and upregulate its expression as previously described (Tan *et al.*, 2001). Conversely, exogenous application of TGF-β1 on a skin wound at day 2 following the injury had opposite effects, with PPARβ expression prematurely downregulated (Figure 1). As a consequence there was a decrease in PKBα/Akt1 activity and a transient but significant delay in wound closure (Tan *et al.*, 2005).

In summary, spatial and temporal effects mediated by cytokines modulate the response of keratinocytes during a stress situation such as skin injury. Cytokines, such as TNF-α and TGF-β1, are mainly produced by the cells populating the wound bed. They attract and activate surrounding keratinocytes that proliferate and migrate through the provisional matrix temporarily deposited in the clot. Activated keratinocytes produce TNF-α that stimulates the expression of PPARβ via the SAP-kinase pathway, until TGF-β1 antagonizes this effect and suppresses PPARβ expression. This temporal regulation is a key process in regenerating epithelium.

INVOLVEMENT OF PPARβ IN HAIR FOLLICLE MORPHOGENESIS

When reactivated in interfollicular epithelium following injury, PPARβ plays important roles in the response of keratinocytes to stress. In the hair follicle, PPARβ is constitutively expressed, and, like many other nuclear hormone receptors, has a role in normal hair follicle development (Michalik *et al.*, 2001; Alonso and Rosenfield, 2003; Di-Poi *et al.*, 2005). Hair follicle morphogenesis depends on epithelium–mesenchyme interactions (Alonso and Rosenfield, 2003) and on hormonal signalling, which is important in modulating hair cycling from anagen to telogen. PPARβ regulates postnatal hair growth, but not the initiation of hair morphogenesis, as the total number of hair follicles is similar in PPARβ$^{+/+}$ and PPARβ$^{-/-}$ mice (Di-Poi *et al.*, 2005). However, a lower hair score for hair follicle morphogenesis in PPARβ$^{-/-}$ compared to PPARβ$^{+/+}$ mice showed that PPARβ is required for hair follicle growth. In agreement with this observation, treatment of skin organ cultures with a PPARβ agonist increases the hair score in PPARβ$^{+/+}$ but not in the PPARβ$^{-/-}$ explants. Developing hair follicles of PPARβ-deficient mice at postnatal day 4 (P4) display an increased amount of apoptotic keratinocytes compared to their wild-type counterparts, in which apoptotic keratinocytes are restricted to the suprabasal layers of the interfollicular epidermis (Figure 2b). Consistent with the known function of PPARβ in regulating the activity of PKBα/

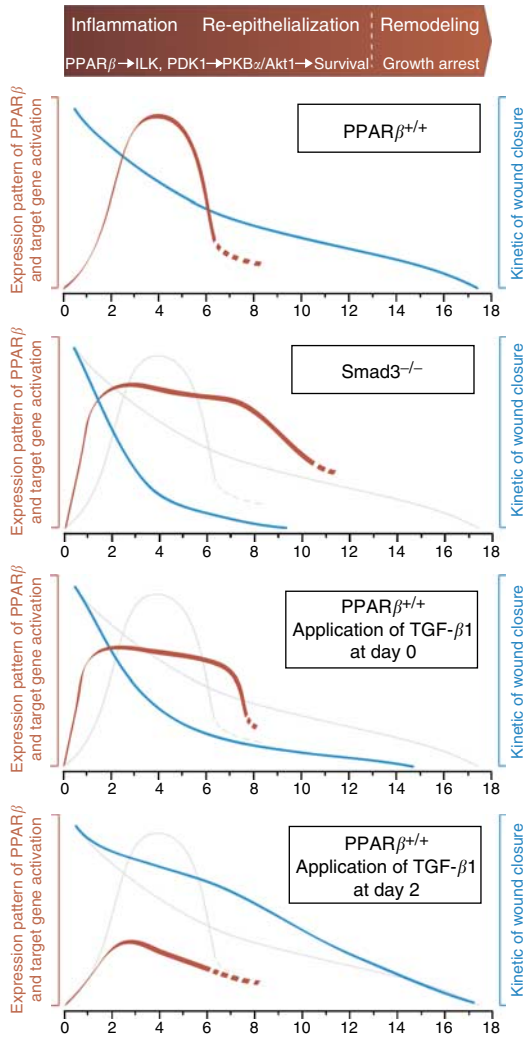

Figure 1. Overview of the consequences of the crosstalk between PPARβ and the TGF-β1 pathway in skin repair. Upon injury pro-inflammatory cytokines such as TNF-α are produced by the infiltrating immune cells contributing to PPARβ re-expression in the interfollicular epidermis through an AP-1 response element in PPARβ promoter (Tan *et al.*, 2001). Activated PPARβ regulates the expression of integrin-linked kinase and 3-phosphoinositide-dependent kinase-1, which contributes to PKBα/Akt1 activation by phosphorylation to protect keratinocytes from apoptosis (Di-Poi *et al.*, 2002). Along with the wound-repair progression into the re-epithelialization and remodelling phase, both wound fibroblasts and immune cells produce TGF-β1. Through the activation of the TGF-β1/Smad3 pathway, TGF-β1 antagonizes the TNF-α effect by preventing the binding of cJUNp300 on the AP-1 site in the PPARβ promoter (Tan *et al.*, 2004). As illustrated in the graphic representation of wound closure, delayed repression of PPARβ expression obtained through genetic ablation of Smad3 accelerates wound healing, whereas its inhibition following topical application of TGF-β1 at day 2 after injury leads to a transient delay in wound closure. Alternatively, early exposure to TGF-β1 at day 0 following injury leads to a prolonged expression of PPARβ and accelerated wound repair probably due to increased recruitment of inflammatory cells by TGF-β1. Blue lines represent the kinetics of wound closure, red lines represent PPARβ expression. Gray lines on each graph are a reminder of the wild-type pattern of both PPARβ expression and kinetics of wound closure.

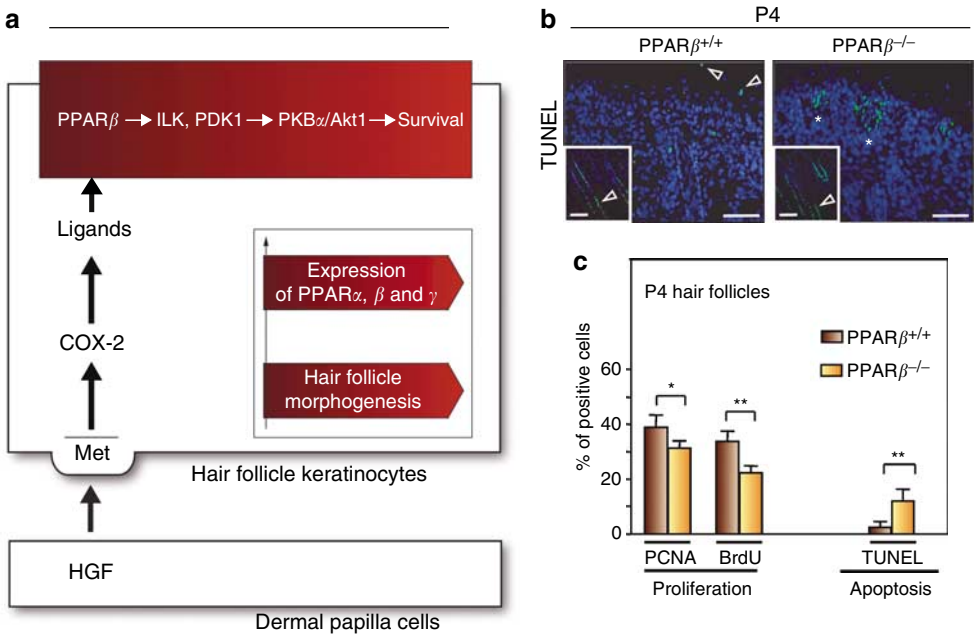

Figure 2. **PPARβ in hair follicle morphogenesis.** (**a**) PPARβ is constitutively expressed in hair follicles. It is transiently activated by ligands produced during hair follicle morphogenesis via COX-2 activation. COX-2 is activated in hair follicle keratinocytes via the paracrine effect of hepatocyte growth factor (HGF) through its receptor Met. (**b**) As described for wound repair, PPARβ expression and activation during morphogenesis protects hair follicle keratinocytes from apoptosis. The TUNEL assay revealed an increased number of apoptotic cells in developing hair follicles from PPARβ$^{-/-}$ mice (day 4 postnatal P4, hair follicles at stage 1–4 according to the classification by Paus *et al.*, 1999). (**c**) Quantification of proliferative and apoptotic cells in developing hair follicles at day P4: PPARβ$^{-/-}$ hair follicle keratinocytes, compared to their wild-type counterparts display less proliferation and increased apoptosis as revealed by proliferating cell nuclear antigen (PCNA)/5-bromodeoxyuridine staining (BrdU) and TUNEL assay, respectively.

Akt1 (Di-Poi *et al.*, 2002), and with the role of PKBα/Akt1 in hair follicle morphogenesis (Rosenfield *et al.*, 2000), the spatio-temporal activation of PPARβ in the developing hair follicles protects keratinocytes from apoptosis via the PKBα/Akt1 pathway. PKBα/Akt1 activity in PPARβ$^{+/+}$ skin is reflected in the increase of the phosphorylation of antiapoptotic factors, such as FKHR and Bad. In PPARβ$^{-/-}$ skin, this activation is postponed until P7. These data show that the delay in hair follicle morphogenesis seen in the skin of PPARβ$^{-/-}$ mice is the consequence of a reduced antiapoptotic activity of PKBα/Akt1. In addition, a slight decrease in the number of proliferative cells was also observed in the PPARβ$^{-/-}$ mice compared to the wild-type skin.

Although PPARβ is expressed constitutively in hair follicles at all stages of their morphogenesis, it seems to be important only for hair follicle elongation (P4), which suggests that a PPARβ ligand is produced at that time. Cyclooxygenase-2 (COX-2) is known to produce arachidonic acid derivatives that are potent ligands of PPARβ. Moreover, COX-2 was shown to be active in the developing hair follicles (Muller-Decker *et al.*, 2003), where its stimulation parallels the action of PPARβ. In fact COX-2 expression is upregulated in hair follicle keratinocytes from P1 to P4 by dermal signals produced by the dermal papilla (Millar, 2002; Zeng *et al.*, 2002). In line with this expression pattern, the COX-2-specific inhibitor (NS-398) delays hair follicle morphogenesis in a dose-dependant manner when applied to PPARβ$^{+/+}$ but not to PPARβ$^{-/-}$ skin explants (Di-Poi *et al.*, 2005). Moreover, hepatocyte growth factor treatment increases COX-2 expression in both PPARβ$^{+/+}$ and PPARβ$^{-/-}$ keratinocytes in a dose-dependent manner. Importantly, exposure of PPARβ$^{+/+}$ keratinocytes to hepatocyte growth factor leads to an increase in the activity of PPARβ, as reflected by increased expression levels of 3-phosphoinositide-dependent kinase-1 and integrin-linked kinase, and increased phosphorylation of PKBα/Akt1 (Di-Poi *et al.*, 2005).

In summary, hepatocyte growth factor produced by the dermal papilla fibroblasts triggers a temporal induction of COX-2 activity in hair follicle keratinocytes. COX-2 in turn activates PPARβ via ligand production. The subsequent activation of the PKBα/Akt1 pathway protects hair follicle keratinocytes from premature apoptosis, thus enabling them to participate in normal hair follicle morphogenesis (Di-Poi *et al.*, 2005) (Figure 2).

CONCLUSION

The expression pattern of PPARα and PPARβ in mouse epidermis suggests a dual role for these nuclear hormone receptors involved both in skin development and in repair after an injury. While both receptors are constitutively expressed in the hair follicles, they remain undetectable in the normal adult mouse interfollicular epidermis, in contrast to their expression in the embryonic epidermis. A full thickness injury of the adult skin induces a strong re-activation of PPARα and PPARβ expression in these cells.

Genetically engineered PPARα$^{-/-}$, PPARαΔ13, PPARβ$^{+/-}$, and PPARβ$^{-/-}$ mice were valuable tools in deciphering the roles of PPARα and PPARβ in the mechanisms of skin wound

repair. PPARα$^{-/-}$ and PPARαΔ13 mice display a transient delay in wound closure that overlaps with the inflammatory phase of healing. This delay correlates with the impaired recruitment of inflammatory cells to the wound bed of injured PPARα$^{-/-}$ mice. It is most probably due to a keratinocyte-dependent defect since it was also observed in PPARαΔ13 mice that present an exacerbated production of TNF-α after an injury. These two observations converge in suggesting an impaired inflammatory response in both types of mutant animals. They lend support to the notion that PPARα controls the inflammatory phase of skin repair. TNF-α was found to be the trigger of inflammation-induced expression and activation of PPARβ in the wounded epithelium via both the activation of the AP-1 transcription factor complex that binds to a response element in a PPARβ promoter, and the production of an endogenous PPARβ ligand. An opposing signal from the TGF-β1 pathway converges at the same AP-1 response element leading to a decrease in PPARβ expression at the later stages of repair. During the window of PPARβ expression and activation controlled by the timely secretion of TNF-α and TGF-β1 by immune cells and myofibroblasts, respectively, keratinocytes are protected from cell death via the activation of the PKBα/Akt1 pathway.

In addition to this stress response, epithelial–mesenchymal interactions are also involved in the mechanisms of hair follicle development. During hair follicle morphogenesis, fibroblasts from the dermal papilla produce the paracrine growth factor hepatocyte growth factor to which hair follicle keratinocytes respond by stimulation of the COX-2 gene. Enhanced COX-2 levels lead to increased PPARβ ligand production. In this case, timely activation of the constitutively expressed PPARβ induces the PKBα/Akt1 pathway that protects follicular keratinocytes from premature apoptosis. In conclusion, PPARα and PPARβ are key regulators of skin homeostasis. They control repair after an injury, and participate in normal hair follicle morphogenesis.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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