Alexandra Montagner and Walter Wahli*

Contributions of peroxisome proliferator-activated receptor β/δ to skin health and disease

Abstract: Among the three peroxisome proliferator-activated receptor (PPAR) transcription factors, PPARβ/δ is the isotype with the broadest expression pattern. In fact, the expression of PPARβ/δ is ubiquitous, albeit at levels that are tightly regulated. Herein, we reviewed its multiple functions in skin health and disease. PPARβ/δ has pro-differentiating effects in keratinocytes, regulates sebocyte differentiation, and promotes hair follicle growth in healthy skin. Furthermore, we reviewed novel insights into the roles of PPARβ/δ in skin wound healing, especially in inhibiting apoptosis and in modulating keratinocyte proliferation and migration. Therefore, PPARβ/δ represents a research target for the understanding and treatment of inflammatory skin diseases, such as psoriasis and acne vulgaris. In addition, PPARβ/δ is a tumor growth modifier. Epidemiological studies have established that tumor progression may be exacerbated by chronic low-grade inflammation, a condition promoting the production of the lipids that act as modulators of PPARβ/δ activity. The action of PPARβ/δ in skin cancer is ambivalent, which might be explained by this receptor's putative highly context-specific behavior, which depends on a combination of factors ranging from receptor expression levels to co-regulator distribution, diversity and activity of the ligands produced, and other tissue-specific conditions. Given its diverse and crucial roles in many tissues and organs, PPARβ/δ will remain a major focus of future research.

Keywords: keratinocytes; non-melanoma skin cancer; nuclear receptors; psoriasis; wound healing.

***Corresponding author: Walter Wahli,** Center for Integrative Genomics, National Research Center Frontiers in Genetics, University of Lausanne, CH-1015 Lausanne, Switzerland, e-mail: walter.wahli@unil.ch

Alexandra Montagner: Center for Integrative Genomics, National Research Center Frontiers in Genetics, University of Lausanne, CH-1015 Lausanne, Switzerland; and Toxicology and Integrative Metabolism, INRA ToxAlim, 180 Chemin de Tournefeville, 31027 Toulouse Cedex 3, France

Introduction

The skin is the largest organ of the body with respect to weight and surface area. The outer layers of cells in the skin compose the epidermis, which together with the dermis forms the cutis. In the latest stages of fetal development, the epidermis develops into a fully stratified and differentiated epithelium that undergoes continuous renewal after birth. In fact, the basal layer of this stratified tissue contains undifferentiated proliferating keratinocytes that undergo a differentiation program as they migrate from the basal to the uppermost layer of the epidermis. The basal layer is the source of skin cells throughout life, which are generated through asymmetrical division (1, 2). This cell layer is maintained through several autocrine and paracrine acting factors, which are important for epidermal homeostasis (3–5). The vectorial differentiation program of keratinocytes comprises the processing of lipids [sphingolipids, free fatty acids (FAs), and cholesterol] and the sequential expression of structural proteins (keratins, involucrin, loricrin, and filaggrin), which are each essential to the protective function of the epidermis. In fact, the outermost layer of the epidermis, the stratum corneum, consists of a layer of cross-linked proteins and lipids and dead keratinocytes (corneocytes), which form an efficient barrier against water loss, microorganism invasion, mechanical damage, and chemical poisoning. The stratum corneum is also where desquamation, the natural process by which dead outer skin cells are sloughed away and replaced, occurs (6). Epidermal homeostasis and the integrity of the barrier function depend on a well-tuned coordination of keratinocyte proliferation, differentiation, positioning in the tissue, and apoptosis.

As in other organs, lipid signaling contributes to skin health and disease. The nuclear receptors called peroxisome proliferator-activated receptors (PPARs) are key mediators of lipid signaling. They sense diverse lipophilic molecules that act as ligands and thereby link fluctuations in the levels and distribution of FAs, eicosanoids, and some phospholipids to differential gene expression (7, 8). There are three related PPAR isotypes that compose a small subfamily of nuclear receptors: PPARα (NR1C1), PPARβ/δ (NR1C2), and PPARγ (NR1C3) (9). The transcriptional activity of all three of them is mediated by PPAR:retinoid X receptor heterodimers that bind to specific DNA sequence elements termed peroxisome proliferator response elements. By doing so, they

regulate the expression of genes implicated in several important processes, such as lipid and carbohydrate metabolism, tissue repair, vascular biology, and sexual dimorphism, as well as in more general basic cellular processes, such as proliferation, differentiation, and migration (10, 11).

The expression patterns of PPARα, PPARβ/δ, and PPARγ are well described (10, 12, 13). Although presenting some specificity, they are also overlapping, with distinct expression levels. PPARα, which has been well described in FA catabolism, is highly expressed in brown adipose tissue, heart, liver, kidney, and intestines, whereas PPARβ/δ is relatively abundant in the brain, skeletal muscle, gut, placenta, and skin. The third isotype, PPARγ, is expressed as two isoforms, γ1 and γ2. PPARγ1 is 28 and 30 amino acids shorter at its N-terminus than PPARγ2 in rodents and humans, respectively. PPARγ1 also has a broader expression pattern, which includes immune cells, brain, gut, and endothelial cells, whereas PPARγ2 is found mainly in adipose tissues. This list is not exhaustive; a more detailed description of PPAR expression can be found in previous articles (10, 12–14).

In recent years, PPARs (and especially PPARβ/δ) have emerged as having multifaceted key roles in skin health and disease (Figure 1). Characterized natural PPARβ/δ ligands are unsaturated FAs, saturated FAs (weak), prostacyclin, 4-hydroxy-2-nonenal, 4-hydroxydodeca-(2*E*,6*Z*)-dienal, and very low-density lipoprotein components (15). The present review summarizes our current knowledge of PPARβ/δ functions in rodent and human skin, including embryonic development, the maintenance of adult skin and skin appendages, and normal skin repair. We also discuss the implication of PPARβ/δ in skin pathologies, such as hyperproliferative and inflammatory diseases, and cancer.

Skin development: cell differentiation, epidermis, and appendages

The three PPAR isotypes are expressed in rodent and human skin. Cell culture and *in vivo* approaches have demonstrated that PPARβ/δ has pro-differentiating effects in keratinocytes in normal and inflammatory conditions, regulates hair follicle growth, and promotes sebocyte differentiation.

In keratinocytes from adult human epidermis, PPARβ/δ is constitutively expressed and is present throughout all epidermal layers (16–18). In contrast, in the interfollicular epidermis of rodents, PPARβ/δ is expressed at relatively high levels during development and much less in the adult epidermis (19). In mouse keratinocytes, PPARβ/δ expression can be down-regulated by C/EBPα and C/EBPβ through a mechanism that requires both the binding of C/EBP to the promoter of the PPARβ/δ gene and histone deacetylation. We propose that such interplay between PPARβ/δ and C/EBP transcription factors is crucial to the molecular control of the balance between differentiation and proliferation (20). Furthermore, keratinocyte fatty acid binding protein (K-FABP) is essential to the ability of PPARβ/δ to properly induce keratinocyte differentiation. Hence, the tissue-specific expression of particular FABPs may support the tissue-specific functions of PPARs, which raises the intriguing possibility that the same K-FABP–PPARβ/δ pair plays a similar role in mediating the differentiation of other cell types in which both factors are expressed concomitantly

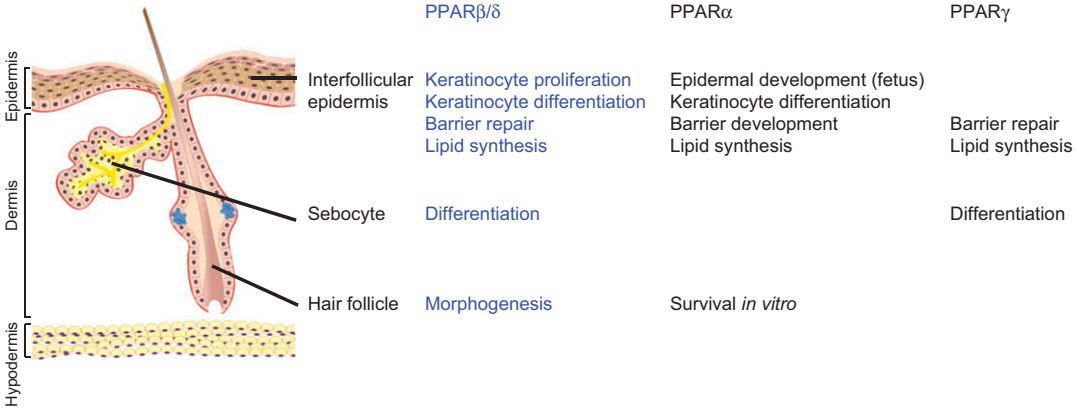

Figure 1 Functions of PPARs in the epidermis and epidermal appendages.
This schematic outlines the skin structures and functions of PPARs in the interfollicular epidermis, sebocytes, and hair follicles. Observations obtained after activation of PPARs by their specific ligands in three skin structures are summarized (see text for references).

(21). The pro-differentiating action of ligand-activated PPARβ/δ is keratinocyte-autonomous and mediated by an indirect mechanism that involves the transcriptional regulation of adipocytokine angiopoietin-like 4 (ANGPTL4) and the subsequent activation of protein kinase C and activator protein 1 (AP-1) transcription factors (22).

Hair follicle morphogenesis depends on a strictly controlled balance between keratinocyte proliferation, differentiation, and apoptosis. PPARβ/δ is expressed in the hair follicles of both fetal and adult skin. Furthermore, follicle morphogenesis involves complex bidirectional interactions between the keratinocytes and the underlying mesenchyme. These interactions involve hepatocyte growth factor (HGF), which is produced by dermal papilla cells during early hair follicle development. HGF stimulates cyclooxygenase-2 (COX-2) expression in keratinocytes, which results in the activation of PPARβ/δ and the subsequent stimulation of the protein kinase Bα (PKBα)/Akt1 pathway at a specific stage of hair follicle development. However, in contrast to inflammatory cytokines that regulate both PPARβ/δ expression and activation, HGF is implicated only in PPARβ/δ activation. Interestingly, HGF is a versatile modulator of cell proliferation, migration, differentiation, and apoptosis. It has been implicated in mesenchyme-epithelium interactions in several tissues and has been attributed functions in the morphogenesis of other ectodermal structures, such as teeth and feathers, which may therefore also require PPARβ/δ activity (23).

In brief, activation of PPARβ/δ by COX-2-derived ligands protects hair peg keratinocytes against apoptosis, promoting normal hair follicle development (24).

Each PPAR isotype is expressed in the basal layer of the sebaceous gland, and ligand activation of each isotype increases lipogenesis (25). The gland comprises sebocytes that are epithelial cells, which accumulate neutral fat droplets during terminal differentiation. Sebocyte lysis releases lipids/sebum into the hair follicle canal, through which they reach the surface of the skin where they prevent drying of the skin and hair (26). Interestingly, PPARβ/δ seems to be important in the late stages of sebocyte differentiation (27), in contrast to its implication in the early phase of adipocyte differentiation in adipose tissues (28). The meaning of this stage-specific effect on the differentiation of two lipogenic cell types remains to be unveiled.

Skin lipid metabolism

As mentioned above, the permeability barrier resides in the stratum corneum and comprises lamellar membranes enriched with extracellular neutral lipids surrounding the corneocytes (29, 30). These extracellular lipids differ from the lipids that constitute most biological membranes. Their total lipid mass comprises approximately 25% cholesterol, 50% ceramides, and 15% free FAs (31). Mice devoid of PPARβ/δ displayed delayed recovery of the permeability barrier, suggesting that this PPAR isotype has a physiologic function in permeability barrier homeostasis. This delay in barrier recovery was most likely due to the decreased synthesis and secretion of lamellar bodies, as well as reduced numbers of extracellular lamellar membranes in the stratum corneum (32).

Treatment of both cultured human keratinocytes and mouse epidermis with a selective PPARβ/δ ligand (GW1514) increased the accumulation of lipids that were predominantly triglycerides, but did not stimulate the conversion of keratinocytes to sebocytes or adipocytes. It is not yet clear why lipid accumulation is increased in these cultured keratinocytes or whether this *in vitro* observation has functional significance *in vivo* (33).

Skin wound healing

The formation of a new epithelium after a skin injury is part of a healing process that is often lifesaving. The initial stage of this process is an immediate inflammatory response to the injury. Next, keratinocytes migrate and proliferate to cover the wound bed in the *sensu stricto* reepithelialization event. The proliferation of fibroblasts from the dermis also contributes to the healing process, as does the production of novel blood vessels that irrigate the repaired skin. In rodents, PPARβ/δ expression is extremely low in the interfollicular adult epidermis, but is strongly reactivated and remains relatively high in keratinocytes at the edges of wounds as long as the entire repair process has not been completed (19). The injury-associated stimulation of PPARβ/δ is mediated by the activation of the stress-associated protein kinase pathway by inflammatory cytokines that are released after the injury, such as tumor necrosis factor-α (TNF-α) (Figure 2) (34). Concomitantly, the production of an endogenous ligand (or multiple ligands) is induced, which is a prerequisite for activation of the receptor in the keratinocytes (34). The expression of PPARβ/δ is maximal during the inflammatory phase and is then progressively reduced during reepithelialization to finally reach levels observed in the unwounded skin, once cicatrization has been achieved. The down-regulation of PPARβ/δ depends on the inhibition of AP-1 binding to the PPARβ/δ promoter, which

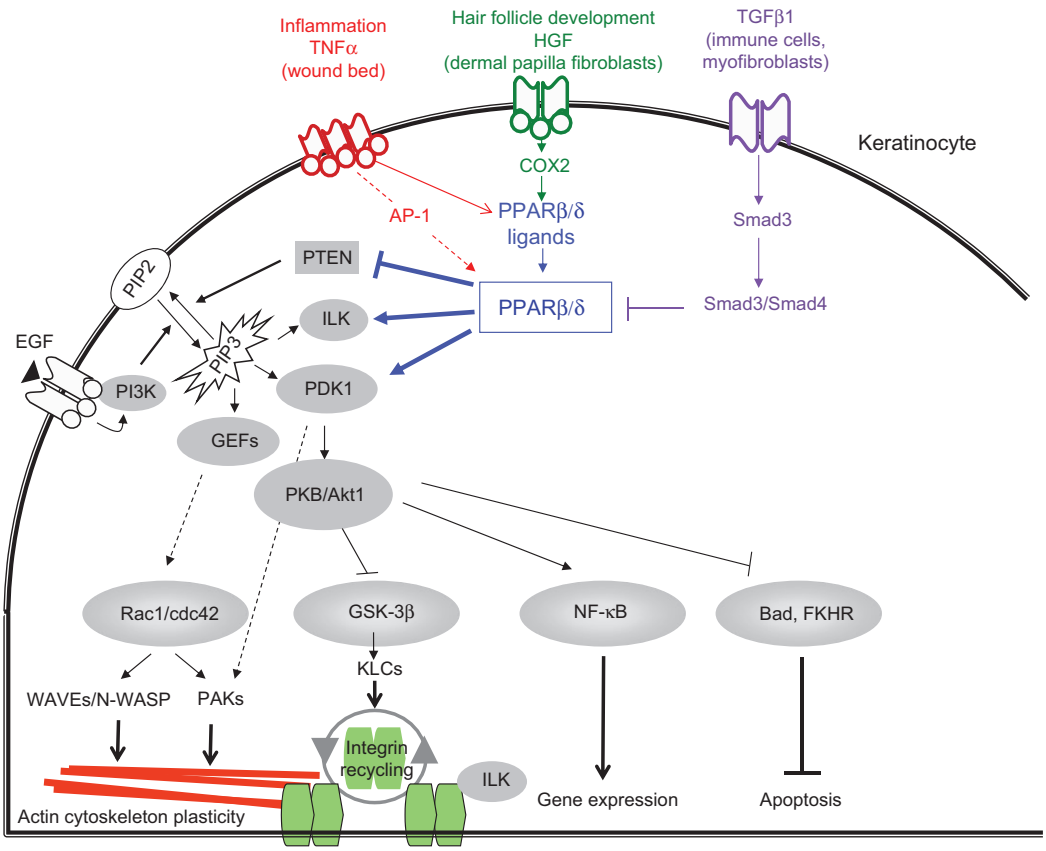

Figure 2 Roles of PPARβ/δ in skin wound healing.
The expression of the *Ppar*β/δ gene is stimulated by the AP-1 transcription factor complex, which is activated by the stress-associated protein kinase pathway triggered by pro-inflammatory cytokines such as TNF-α. TNF-α also induces the production of PPARβ/δ ligands in the injured epithelium. Ligands can also be produced during hair follicle development by COX-2-mediated HGF signaling. Activated PPARβ/δ down-regulates *Pten* expression and stimulates the genes that encode integrin-linked kinase (ILK) and 3-phosphoinositide-dependent kinase-1 (PDK1). The latter results in activation through the phosphorylation of PKBα/Akt1, which increases the inhibitory phosphorylation of BAD (BCL2-associated agonist of cell death), FKHR (forkhead transcription factor Foxo1), and GSK-3β (glycogen synthase kinase 3β), causing reduced apoptosis and increased gene expression and integrin recycling. As epithelialization proceeds, TNF-α-induced *Ppar*β/δ expression is progressively repressed by Smad3/Smad4 complex-mediated TGFβ1 signaling, which inhibits AP-1 binding to the *Ppar*β/δ promoter. Increased levels of PIP3 (phosphatidylinositol 3,4,5-trisphosphate) and PDK1 affect the cytoskeleton, which is implicated in directional sensing and cell migration.

is controlled by transforming growth factor β1 (TGFβ1) (35). The completion of skin repair is delayed by 2–3 days in PPARβ/δ-deficient mice (19), which underscores the importance of this transcriptional regulator in wound healing. In fact, PPARβ/δ activates the phosphoinositide 3-kinase (PI3K)/PKBα/Akt1 (PI3K/PKBα/Akt1) pathway, which promotes keratinocyte survival at the wound edges (24). Furthermore, it favors keratinocyte adhesion and migration, which promotes reepithelialization (19, 36) (Figure 2).

To understand the functional interaction between PPARβ/δ and TGFβ1, topical application of recombinant TGFβ1 (TGFβ1 pathway gain of function) and Smad3 (mothers against decapentaplegic homolog 3) deficiency (TGFβ1 pathway loss of function) were used (37). Manipulating TGFβ1 activity in the epidermis of the wounds induced prolonged PPARβ/δ expression and activity, which resulted in accelerated wound closure. This result suggested that PPARβ/δ expression and activity correlate with healing efficiency. Such knowledge about how TGFβ1 regulates PPARβ/δ during wound healing may help improve treatments for chronic wound disorders.

Moreover, gene expression profiling in wild type and PPARβ/δ-deficient primary keratinocyte cultures revealed similar amounts of genes stimulated or repressed by PPARβ/δ. Comparative analysis of expressed genes confirmed PPARβ/δ functions in cell proliferation, differentiation, migration, and adhesion (11). Of particular interest,

the most deregulated genes were genes previously implicated in cell proliferation, tumor growth, and angiogenesis (38–40). For instance, three of these genes, *Akt1*, *Cxcl12*, and *Src*, regulate the PI3K and mitogen-activated protein kinase (MAPK) pathways, both of which have been implicated in skin wound healing. In brief, PPARβ/δ deficiency in keratinocytes affected gene expression, which may explain the phenotypic changes observed during skin wound healing in PPARβ/δ-deficient mice (11).

The regeneration of the epithelium to close a wound depends on a contribution from the underlying dermal tissue, particularly fibroblasts and fibroblast-like cells, called fibrocytes, derived from the bone marrow (Figure 3) (41, 42). Regulation of the crosstalk between keratinocytes and fibroblasts is central to preventing either insufficient or excess wound repair. Notably, keratinocyte proliferation after an injury must be fine-tuned for reepithelialization (43). Interestingly, PPARβ/δ deficiency caused epidermal hyperproliferation in early wound repair, upon hair plucking, or in response to a topical challenge with the phorbol ester 12-*O*-tetradecanoylphorbol-13-acetate (TPA) (19, 44). During wound healing, this keratinocyte proliferation is under the control of fibroblasts that produce mitogenic factors whose genes are under the control of AP-1, which is itself under the upstream regulation of the interleukin 1 (IL-1) released by keratinocytes at the site of injury (Figure 3). In parallel, activated PPARβ/δ in fibroblasts increases the production of the secretory IL-1 receptor antagonist (sIL-1Ra), resulting in the autocrine down-regulation of IL-1 signaling. As a consequence, the production of secreted mitogenic factors by the fibroblasts is reduced and the proliferation of keratinocytes is down-regulated (43). Together, these findings revealed a novel paracrine effect of PPARβ/δ on epithelial cell growth, which might also operate in other organs in addition to skin. Thus, PPARβ/δ controls keratinocyte differentiation,

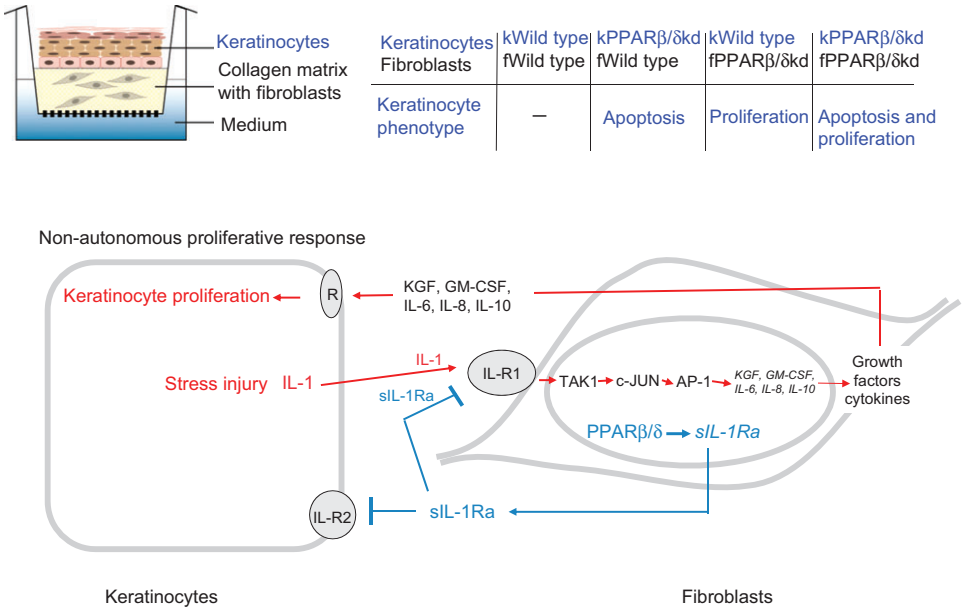

Figure 3 Non-cell-autonomous control of keratinocytes by PPARβ/δ.
Organotypic cultures [OTCs; (79); see scheme] with primary human keratinocytes and fibroblasts were grown with control or PPARβ/δ knockdown keratinocytes (kWild type vs. kPPARβ/δkd) and fibroblasts (fWild type vs. fPPARβ/δkd). kPPARβ/δkd presented increased apoptosis, whereas fPPARβ/δkd potentiated keratinocyte proliferation. OTC with both kPPARβ/δkd and fPPARβ/δkd exhibited increased keratinocyte proliferation and apoptosis (43). Keratinocyte proliferation is regulated by a nonautonomous paracrine mechanism. IL-1 produced by keratinocytes activates c-Jun through IL-1 receptor type 1 (IL-R1) and transforming growth factor β-activated kinase 1 (TAK1) in dermal fibroblasts. c-Jun is an obligate partner of the AP-1 transcription complex, which stimulates the expression of mitogenic factors [keratinocyte growth factor (KGF), granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-6, IL-8, IL-10] secreted by the fibroblasts. In these cells, PPARβ/δ attenuates IL-1 signaling through the stimulation of sIL-1Ra production; the gene that encodes sIL-1Rra is a direct PPARβ/δ target. sIL-1Ra has little affinity for IL-1R2, which is highly expressed in keratinocytes. However, it binds with high affinity to IL-1R1 expressed by the fibroblasts. Therefore, sIL-1Ra acts as an autocrine antagonist of IL-1 signaling in fibroblasts. The binding of sIL-1Ra to IL-1R1 down-regulates IL-1-mediated signaling events and, consequently, the production of several AP-1-mediated mitogenic factors. This mechanism leads to reduced keratinocyte proliferation. Therefore, the absence of PPARβ/δ in fibroblasts results in increased keratinocyte proliferation (43).

survival, and migration, as well as keratinocyte proliferation by cell-autonomous and nonautonomous pathways.

Skin diseases

Psoriasis

Psoriasis is an inflammatory skin disorder in which epidermal hyperproliferation and abnormal keratinocyte differentiation are major characteristics. It affects 1–2% of the population in the USA and is often debilitating. PPARβ/δ is increased in psoriatic areas, most likely through inflammatory signals as previously described after a skin injury (45). A transgenic murine model allowing PPARβ/δ activation in the epidermis sustained an inflammatory skin disease similar to psoriasis, with keratinocyte hyperproliferation, dendritic cell accumulation, and endothelial activation (45). This response required the activation of the Th17 subset of T cells, known to be central to psoriasis. Key transcriptional programs of psoriasis, such as cholesterol synthesis and IL-1-related signaling, were replicated in this model, suggesting that PPARβ/δ might regulate these changes in psoriasis. Furthermore, phosphorylation of signal transducer and activator of transcription 3 (STAT3) was enhanced by PPARβ/δ, whereas inhibition of STAT3 phosphorylation blocked disease development, implicating PPARβ/δ in this process (45). Interestingly, PPARβ/δ was also expressed in activated human T cells isolated from psoriatic skin lesions, where it is induced by stimulation with type 1 interferon (IFN). This study suggested that the induction of PPARβ/δ by type 1 IFN contributes to the prolongation of activated T cells in psoriasis-affected skin (46). Using the same murine model as above, it was shown that three selective PPARβ/δ antagonists formulated for topical application to the skin demonstrated efficacy in reducing psoriasis-like changes triggered by PPARβ/δ activation. One of these compounds, an irreversible PPARβ/δ antagonist (GSK3787), retained efficacy when applied topically only three times per week. Collectively, these observations suggested the clinical usefulness of topical inhibition of PPARβ/δ to treat psoriasis, which deserves further exploration (47). In this experimental model of psoriasis triggered by PPARβ/δ overexpression, one can argue that inhibiting PPARβ/δ logically suppresses the origin of the disease. Thus far, PPARβ/δ antagonists have not been evaluated on psoriasis models not induced by experimental PPARβ/δ overexpression, and antipsoriasis drugs have not been applied to the PPARβ/δ-induced disease model. In contrast to these encouraging results obtained with PPARβ/δ antagonists, a pilot study with psoriatic patients showed that the PPARβ/δ agonist tetradecylthioacetic acid did not exhibit beneficial effects when topically applied on plaque psoriasis (48). This finding comes as no surprise, given the rather psoriasis-promoting characteristics of PPARβ/δ described above.

Atopic dermatitis

Atopic dermatitis (AD) is an inflammatory, chronically relapsing, noncontagious, and pruritic dermatosis that is linked to alterations of the stratum corneum (49, 50). Little is known about the putative link between PPARβ/δ and AD. In the oxazolone-induced AD-like model in hairless mice, topical application of a PPARβ/δ activator (GW0742) reversed clinical dermatosis, improved barrier function, and increased stratum corneum hydration. These results suggest that topical applications of certain activators/ligands of PPARβ/δ may be worth testing as AD treatment in human subjects (50). Thus, in contrast to psoriasis, for which PPARβ/δ antagonists were beneficial in experimental models, AD treatment might benefit from PPARβ/δ agonists. However, it is important to note that there are no human data so far and the data discussed above are from an experimental mouse model that shows only a few similarities with human AD.

Acne

Acne is a common skin condition characterized by spots that range from mild to inflamed pus-filled pustules and cysts. When long-lasting, it can lead to scarring. Sebum secretion can be considered the major factor responsible for acne, even if seborrhoea *per se* is not a sufficient condition for its development. Current studies concentrate on the factors that regulate sebum composition and secretion. Differences in the type, amount, and arrangement of FAs in the sebum lipids have been reported in acne patients. Unsurprisingly, a number of lipid mediators that have been shown to be PPAR ligands impact sebocyte lipid synthesis and metabolism (51). In fact, increased sebum levels combined with follicular hyperkeratinization are hallmarks of acne vulgaris, and PPARβ/δ was found overexpressed in inflammatory and non-inflammatory acne vulgaris (52). Given that the suppression of sebum secretion correlates with reduced acne, the manipulation of PPAR activity in this condition is worthy of additional exploration.

Among PPAR activators, the PPARβ/δ ligand L-165.041, compared with PPARα and PPARγ ligands, was the most

efficient at inhibiting basal and staurosporine-induced apoptosis in the human sebocyte cell line SZ95 *in vitro*. L-165.041 activated PKB/Akt and p44/42 MAPK, two kinases involved in antiapoptosis activity and proliferation, respectively. The inhibition of these kinases reversed the effect of L-165.041, implicating these pathways in the observed antiapoptotic effect. It was concluded that PPARβ/δ activation might have beneficial effects on acne vulgaris by inhibiting the release of lipids associated with sebocyte apoptosis (53).

Skin cancer

Non-melanoma skin cancer (NMSC)

PPARβ/δ regulates cellular mechanisms that have been recognized as pro- or anticancer, such as cell survival, migration, and differentiation. Therefore, whether PPARβ/δ supports or suppresses tumor formation is still being debated (54, 55). Similarly, the implication of PPARβ/δ in NMSC is much discussed (54, 56).

The role of PPARβ/δ in cancer development has remained elusive, most likely because its promoting or repressing effects on the above-mentioned processes are fine-tuned in a context-dependent manner, which thus far has allowed PPARβ/δ to escape a simplistic view of its functions in tumor biology. Two general models have emerged from these studies that attempt to characterize the ambivalent action of PPARβ/δ in tumorigenesis, possibly reflected in the variation in genetic defects among tumors. They have been presented in some detail recently (56).

In the first model, PPARβ/δ expression is mediated by inflammatory signals through the stress-associated protein kinase pathway, in concert with the notion that low-grade inflammation is often associated with tumor initiation and progression. Alternatively, increased PPARβ/δ expression is supported by APC–β-catenin-dependent signaling, which is enhanced in several tumors, especially colorectal carcinomas. An increase in PPARβ/δ level is insufficient for the activation of target genes, which depends on ligand activation of the receptor. Although endogenous ligands that activate PPARβ/δ during tumorigenesis have not yet been identified, they are produced and are likely diverse. Once activated, one effect of PPARβ/δ is the down-regulation of phosphatase and tensin homolog (PTEN), which results in increased AKT phosphorylation, which in turn inhibits apoptosis and up-regulates vascular endothelial growth factor expression, which might promote tumor growth. Furthermore, ANGPTL4, encoded in a previously identified PPAR target gene (57, 58), has been implicated in cancer progression, although evidence that PPARs up-regulate ANGPTL4 directly in tumor cells is still lacking (59). Moreover, at least in colorectal cancer, PPARβ/δ might mediate the prostaglandin E2-induced expression of ANGPTL4 under hypoxic conditions, which are often observed in the tumor environment (60). Importantly, targeted deletion of PPARβ/δ in colonic epithelial cells inhibited azomethane-induced colonic tumorigenesis (61), and PPARβ/δ is a k-Ras target gene that is up-regulated by the Raf/MEK/ERK pathway in cultured intestinal epithelial cells (62). However, in another study, germline deletion of PPARβ/δ increased azomethane colonic carcinogenesis (63). Taken together, these two studies might indicate paracrine effects of PPARβ/δ. Other factors that might have contributed to such contrasting results will be discussed below. Interestingly, analysis of human skin biopsies of premalignant and malignant skin carcinoma documented increased PPARβ/δ expression, which correlated with both increased COX-2 expression, which has been implicated in skin carcinoma development, and increased microvessel density (64–66). Collectively, these studies have implicated PPARβ/δ in skin tumor formation and progression.

In the second model, activated PPARβ/δ promotes terminal epithelial cell differentiation, and therefore cell cycle withdrawal. Furthermore, its anti-inflammatory action might contribute to decreased tumorigenesis (56). Several studies, all from the same group, show that loss of PPARβ/δ function increases chemically induced skin carcinogenesis (67–70). Along the same line, combining ligand activation of PPARβ/δ with inhibition of COX-2 activity increased the efficacy of preventing chemically induced skin tumorigenesis over that of either intervention alone (70). This effect of PPARβ/δ was thought to be mediated by the inhibition of keratinocyte proliferation, mainly through the activity of protein kinase Cα. However, in transgenic mice that overexpress protein kinase Cα, 7,12-dimethylbenz[*a*]anthracene (DMBA)/TPA treatment had no effect on skin tumor susceptibility. Moreover, the induction of skin cancer by DMBA/TPA involves different molecular mechanisms than skin cancer associated with chronic UV exposure, which is largely the more frequent form in humans (71, 72). Notably, tumor initiation with a unique topical dose of the genotoxic carcinogen DMBA primarily induces *Ha-Ras*-activating mutations, whose frequency only reaches 10–20% in human NMSCs (73–75). In this context, many upstream signaling pathways involved in skin cancer establishment that might be regulated by PPARβ/δ could be blinded by mutations such as those affecting Ha-Ras, thereby masking the impact of

this nuclear receptor on skin cancer in the DMBA/TPA model.

In summary, the opposite pro-differentiation and pro-carcinogenic roles of PPARβ/δ described above may be due to different environmental stimuli, possibly impacting ligand production, and/or different genetic contexts, which could influence PPARβ/δ activities and functions. Furthermore, different mouse genetic models targeting the PPARβ/δ DNA binding domain with a complete loss of PPARβ/δ function or the transactivating domain that might result in a dominant-negative PPARβ/δ were used. All of the above-mentioned variables are likely to affect the expression pattern of numerous PPARβ/δ target genes. Obviously, more work is needed to uncover the determinants of the ambivalent role of PPARβ/δ in tumor development.

Melanoma

Similar to NMSC, the incidence of malignant melanoma is also steadily increasing (76). PPARβ/δ expression has been observed in human melanoma biopsies. Low-dose pharmacological ligand activation of PPARβ/δ in cultured murine and human melanoma cells inhibited cell growth *in vitro*. At the molecular level, this inhibition is due to the direct binding of PPARβ/δ to the Wilms' tumor suppressor (WT1) promoter, which represses its activity, and consequently the growth-stimulating effects of WT1 on these melanoma cells (77).

Expert opinion and outlook

Exploration of the functions of PPARβ/δ remains of highest interest because of its multifaceted roles in major cellular and physiological functions. At the molecular level, PPARβ/δ operates as a ligand-dependent transcription factor that stimulates or represses gene expression. The diversity of functions of this receptor, which range from the control of basic cellular processes to the regulation of complex metabolic functions, represents a major challenge for present and future studies (15). Herein, we have discussed how PPARβ/δ occupies the crossroads of multiple functions in skin biology. From this discussion, PPARβ/δ emerged as a key factor in skin homeostasis and repair. In addition, its implication in several skin diseases identifies it as a target to take into account in the development of novel therapeutic strategies. The similarity of processes involved in tissue repair and tumor development (78) (Table 1), in all of which PPARβ/δ is implicated, underscores how many facets of PPARβ/δ biology remain hidden. Is the difference, if any, between cell proliferation in tissue repair and cell proliferation in tumorigenesis situated in parallel with the PPARβ/δ repressor and activator activity of these processes? The ambivalent roles of this receptor may explain its apparently discordant activities reported in the literature. The debate is not closed, and most likely reflects the difficulty of accurately describing the highly context-specific behaviors of PPARβ/δ, which depend on a combination of factors, including the level of receptor expression, co-regulator distribution, activity of ligand-producing pathways, and others. In particular, a thorough investigation of paracrine signals among the PPARβ/δ-dependent effects on carcinogenesis is still lacking. Thus, a full understanding of context-specific PPARβ/δ activity – in the skin and elsewhere – remains a burning necessity. Hopefully, the availability of diverse new high-throughput technologies allowing global analysis of the interactions between the components of complex biological systems will assist in a step-by-step resolution of today's unsolved problems.

Highlights

- PPARβ/δ is involved in the regulation of key processes in skin biology in fetal and postnatal life.
- PPARβ/δ promotes keratinocyte and sebocyte differentiation and is implicated in hair follicle development.
- The inflammatory response to skin wounds enhances PPARβ/δ expression and triggers the production of PPARβ/δ ligands. Activated PPARβ/δ accelerates wound healing.
- During reepithelialization of the wound bed, PPARβ/δ enhances keratinocyte survival, directional

Wound healing	Cancer
Controlled proliferation	Sustained proliferation
Controlled cell migration (no invasion, no metastasis, no epithelial-mesenchymal transition)	Invasion metastasis (epithelial-mesenchymal transition)
Transient resistance to apoptosis	Resistance to cell death
Angiogenesis and lymphangiogenesis	Angiogenesis and lymphangiogenesis

Table 1 Comparison of the main processes of wound healing and cancer that implicate PPARβ/δ.

sensing, and migration through cell-autonomous mechanisms.
- During wound healing, keratinocyte proliferation is attenuated through the PPARβ/δ-dependent production of sIL-1Ra by skin fibroblasts, which represses the IL-1 signaling that stimulates mitogenic cytokine production and secretion by these cells.
- PPARβ/δ expression is increased in psoriasis, and animal model observations indicate the potential usefulness of its topical inhibition to treat this disease.
- The role of PPARβ/δ in NMSC is ambivalent, and its role in tumor promotion or suppression appears to be context-specific and requires further investigation.

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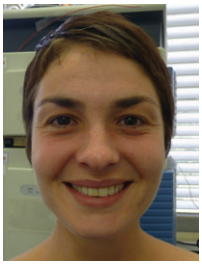

Alexandra Montagner PhD, 2002–2006: Graduate student, Lipoproteins and Lipid Mediators Department, INSERM U563, University of Toulouse, France. 2006–2011: Postdoctoral position, Center for Integrative Genomics, University of Lausanne, Switzerland. 2011–present: Postdoctoral position, Toxicology and Integrative Metabolism, INRA ToxAlim, Toulouse, France.

Walter Wahli PhD, 1980–2002: Full professor and Director Institute of Animal Biology, University of Lausanne (UNIL). 1999–2003: Vice-rector of UNIL (Research, Postgraduate and Continuing Education). 1996–2006: Member of the National Research Council of the Swiss National Science Foundation and Head of the Division Biology and Medicine (2004–2006). 2002–2005: Founding Director, Center for Integrative Genomics, UNIL. 2003–2011: Full professor, Center for Integrative Genomics, UNIL. 2011–present: Professor emeritus UNIL. 2012–present: Visiting Professor, Lee Kong Chian School of Medicine, Imperial College (London) and Nanyang Technological University, Singapore. 2012–present: Member of the council of the Nestlé Foundation for the study of problems of nutrition in the world.