thematic review

*Thematic Review Series: Skin Lipids*

# Peroxisome proliferator-activated receptors and liver X receptors in epidermal biology

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**Abstract The epidermis is a very active site of lipid metabolism, and all peroxisome proliferator-activated receptor (PPAR) and liver X receptor (LXR) isoforms are expressed in the epidermis. Activation of PPARα, -β/δ, or -γ or LXRs stimulates keratinocyte differentiation. Additionally, activation of these receptors also improves permeability barrier homeostasis by a number of mechanisms, including stimulating epidermal lipid synthesis, increasing lamellar body formation and secretion, and increasing the activity of enzymes required for the extracellular processing of lipids in the stratum corneum, leading to the formation of lamellar membranes that mediate permeability barrier function. The stimulation of keratinocyte differentiation and permeability barrier formation also occurs during fetal development, resulting in accelerated epidermal development. PPAR and LXR activation regulates keratinocyte proliferation and apoptosis, and studies have shown that these receptors play a role in cutaneous carcinogenesis. Lastly, PPAR and LXR activation is anti-inflammatory, reducing inflammation in animal models of allergic and irritant contact dermatitis. Because of their broad profile of beneficial effects on skin homeostasis, PPAR and LXR have great potential to serve as drug targets for common skin diseases such as psoriasis, atopic dermatitis, and skin cancer.**—Schmuth, M., Y. J. Jiang, S. Dubrac, P. M. Elias, and K. R. Feingold. **Peroxisome proliferator-activated receptors and liver X receptors in epidermal biology. *J. Lipid Res.* 2008.** 49: **499–509.**

**Supplementary key words** cancer • cutaneous • differentiation • inflammation • permeability barrier • proliferation • transcription factor • skin • stratum corneum

## RELEVANCE OF PPAR AND LXR TARGETING IN SKIN DISORDERS

Several of the most common skin diseases, including psoriasis and atopic dermatitis, are characterized by a spectrum of abnormalities, including inflammation, epidermal hyperplasia, abnormal keratinocyte differentiation, and defects in permeability barrier function. Psoriasis is a chronic skin disorder affecting 2–3% of the population (1–3), whereas atopic dermatitis affects ~5% of the general population and up to 20% of children (4). Atopic dermatitis frequently progresses to mucosal atopy, including asthma and allergic rhinitis ("atopic march"). Although it was long thought that these disorders were solely attributable to immunological defects, increasing evidence is accumulating that primary keratinocyte abnormalities may underlie the pathogenesis of these disorders in many patients. A pertinent example that demonstrates the potential importance of abnormalities in keratinocytes is the recent discovery that many cases of atopic dermatitis are caused by mutations in the filaggrin gene, which is thought to then allow sustained ingress of antigens through a defective barrier, eliciting a characteristic T helper 2 immune response (5–7).

In considering possible strategies to treat these skin disorders, therapies would ideally target as large a spectrum as possible of the abnormalities that commonly occur in these disorders. Drugs that activate the nuclear hormone receptors peroxisome proliferator-activated receptors (PPAR; isoforms: PPARα, PPARβ/δ, and PPARγ) and liver X receptors (LXR; isoforms: LXRα and LXRβ) are potential agents that could have benefits in the treatment of these skin disorders (8–13). In addition, we will also discuss their role in epidermal carcinogenesis, which comprises nonmelanoma skin cancer and malignant melanoma.

*Manuscript received 7 January 2008 and in revised form 8 January 2008.*

*Published, JLR Papers in Press, January 8, 2008.*
*DOI 10.1194/jlr.R800001-JLR200*

Abbreviations: IL-1α, interleukin-1α; LXR, liver X receptor; NF-κB, nuclear factor-κB; PPAR, peroxisome proliferator-activated receptor; RXR, retinoid X receptor; SULT2B1b, sulfotransferase type 2B isoform 1b; TNF-α, tumor necrosis factor-α; TPA, 12-*O*-tetradecanoyl-phorbol-13-acetate; TUNEL, terminal uridine deoxynucleotidyl transferase.

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Cutaneous squamous cell carcinoma and basal cell carcinoma are the two types of nonmelanoma skin cancer that arise from malignant proliferation of keratinocytes and together account for >1 million cases per year in the United States, of which roughly one-quarter is squamous cell carcinoma and three-quarters is basal cell carcinoma; these are the most common cancers in humans (14). Although squamous cell carcinoma and basal cell carcinoma mostly take a locally invasive course and rarely metastasize, malignant melanoma is a highly aggressive cancer that arises from neural crest-derived melanocytes residing in the epidermis. Malignant melanoma commonly metastasizes, which accounts for its high mortality rate (>20%). Incidence rates of all three of these skin cancers, squamous cell carcinoma, basal cell carcinoma, and melanoma, are on the rise (15).

Excellent reviews by others have addressed in detail the potential role of PPAR in wound healing (16, 17); therefore, this will not be discussed in the present review. Additionally, the role of PPAR and LXR in sebaceous gland function has been discussed in detail in another review in this series (18); therefore, it will also not be discussed. Instead, in this review, we will focus on the effects of PPAR and LXR on common inflammatory skin disorders and skin cancer.

## PPAR AND LXR EXPRESSION IN THE SKIN

PPAR and LXR are expressed in the skin (19), with these receptors localizing to a number of different cutaneous sites. Although there is little expression in the dermis in vivo, constitutive expression has been reported for PPARγ, LXRα, and LXRβ in cultured fibroblasts (20, 21). Furthermore, strong expression of PPARα, PPARβ/δ, PPARγ1, LXRα, and LXRβ is present in sebaceous glands (22–26). LXRα and LXRβ are also expressed in sweat gland epithelia. In hair follicles, all PPAR and LXR isoforms have been shown to be expressed not only in the outer root sheath but also in the dermal papilla, connective tissue sheath, and the hair bulb (26–28). Notably, an inverse relationship has been reported between the expression of PPARα and PPARγ and the epidermal progenitor cell marker Tcf3, suggesting an important role in mediating hair follicle differentiation programs. The promoters of PPARα and PPARγ contain Tcf/Lef1 regulatory elements, and Tcf/Lef1 binding represses the expression of their respective target genes (28).

In the interfollicular epidermis of rodents, the PPAR isoforms were initially reported to be transiently expressed during development and not to be expressed in adult epidermis, based on in situ hybridization and immunohistochemistry (23, 29, 30). However, in human adult keratinocytes, all three PPAR isoforms are constitutively expressed (31–33). PPARα and PPARγ are primarily expressed in the suprabasal compartments (i.e., differentiated keratinocytes), whereas PPARβ/δ is present throughout all epidermal layers (32). Furthermore, although both LXRα and LXRβ are expressed in cultured human keratinocytes and throughout all layers of the human epidermis (26, 34), LXRβ is the predominant isoform transcribed in mouse epidermis (35). Finally, all three PPAR isoforms are expressed in human melanocytes in vitro and in epidermal Langerhans cells in vivo (36–38).

## EFFECT OF PPAR AND LXR ACTIVATION ON CUTANEOUS INFLAMMATION

It is well recognized that PPAR and LXR expression is modulated by inflammation both in the epidermis and in other organs, such as the liver, heart, and adipose tissue (39–41). In cultured human keratinocytes, cytokines and ultraviolet light reduced the expression of PPARα, PPARγ, and LXRα, whereas the expression of LXRβ was unchanged and that of PPARβ/δ was increased (42, 43). Moreover, in lesional skin of patients with psoriasis and atopic dermatitis, the expression of PPARβ/δ was also increased, whereas the expression of PPARα and PPARγ was decreased (44, 45) (M. Schmuth, unpublished observation).

To determine the effects of PPAR and LXR activators on cutaneous inflammation, several models have been used. A mouse model measures ear swelling in mice after topically applying 12-*O*-tetradecanoylphorbol-13-acetate (TPA) to the ears, a model of irritant contact dermatitis; a second model measures ear swelling after topical application of an allergen (e.g., oxazolone), first to the abdomen and then several days later to the ears, a model of allergic contact dermatitis. In these models, simultaneous topical treatment with PPARα agonists reduced ear swelling, the magnitude of the inflammatory infiltrate, and the expression of tumor necrosis factor-α (TNF-α) and interleukin-1α (IL-1α) (46, 47). Moreover, PPARα activation inhibited cytokine secretion, maturation, and migration and the T-cell-stimulatory activity of the epidermal antigen-presenting cell, the Langerhans cell. This was associated with decreased levels of phosphorylated nuclear factor-κB (NF-κB) (37). The effects of PPARα agonists were abolished in keratinocytes and Langerhans cells in PPARα-deficient mice, indicating that they are receptor-mediated (37, 46, 47). However, MK886, a noncompetitive inhibitor of PPARα that prevents the conformational changes that allow the binding of PPARα to DNA, only partially restored the effects in Langerhans cells, indicating that DNA binding is only partially responsible for the immune-regulatory effects of PPARα activation on Langerhans cell function (37). Thus, these effects may occur via direct protein-protein interaction with NF-κB. Finally, it has also been reported that topical application of the PPARα activator WY-14643 reduced the ultraviolet light-induced erythema in human skin, which could be secondary to the anti-inflammatory effects (48).

In contrast to PPARα, the effects of PPARβ/δ activators on cutaneous inflammation are less certain. In the mouse model of irritant contact dermatitis (TPA treatment of ears), topical GW1514 decreased the degree of



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inflammation, as determined by ear thickness, ear weight, histology, and myeloperoxidase quantification (43, 49). However, the anti-inflammatory effect did not require PPARβ/δ, because pharmacologic PPARβ/δ activation also reduced myeloperoxidase in the ears of PPARβ/δ-deficient mice, raising the possibility that the observed effects on inflammation are not attributable to PPARβ/δ activation. Additionally, the anti-inflammatory effects required doses much higher than those necessary to induce keratinocyte differentiation (49). On the other hand, PPARβ/δ-deficient mice displayed an increased inflammatory response to TPA treatment (50–52), suggesting that PPARβ/δ in fact plays a role in downregulating inflammation. Clearly, further studies are required to determine whether activators of PPARβ/δ are anti-inflammatory in the skin.

Studies of PPARγ activators have also failed to definitively demonstrate an anti-inflammatory effect in mouse skin. Although the PPARγ agonists ciglitazone and troglitazone have anti-inflammatory properties in both irritant and allergic contact dermatitis mouse models, reducing the production of proinflammatory cytokines, such as TNF-α and IL-1α (53), similar anti-inflammatory properties are seen in PPARγ-deficient mice. These results indicate that the inhibition of cutaneous inflammation by ciglitazone and troglitazone is not necessarily mediated by epidermal PPARγ. This observation is similar to reports in macrophages, in which glitazones also had anti-inflammatory effects independent of PPARγ (54). As with PPARβ/δ, further studies are required to determine whether the activation of PPARγ is anti-inflammatory in the skin.

In contrast, studies have clearly demonstrated that LXR activators have potent anti-inflammatory activity in both the irritant and allergic contact models of cutaneous inflammation (55, 56). Immunohistochemistry demonstrated an inhibition in the production of the proinflammatory cytokines IL-1α and TNF-α in oxysterol-treated sites from both TPA- and oxazolone-treated animals (55). Moreover, LXR activators did not reduce inflammation in LXRβ-deficient or LXRα/β-deficient mice, indicating that LXRβ was required for this anti-inflammatory effect (55). Oxysterols also caused a partial reduction in ear thickness in LXRα-deficient mice (~50% of that observed in wild-type mice), suggesting that this receptor also plays a role in mediating the anti-inflammatory effects (55). Thus, similar to PPARα, activation of LXR inhibits cutaneous inflammation.

## PPAR AND LXR ACTIVATION INDUCES EPIDERMAL DIFFERENTIATION

Keratinocyte differentiation is a complex, sequential process (57, 58) that ultimately results in the formation of the stratum corneum, an epidermal layer consisting of keratinocytes that have lost their nucleus (corneocytes) surrounded by a lipid-enriched extracellular matrix. Corneocytes provide strength and rigidity as a result of the extensive cross-linking of proteins, such as loricrin, involucrin, filaggrin, small-proline-rich proteins, and others, on the inner plasma membrane by the enzyme transglutaminase-1, to form the cornified envelope. In addition, the corneocytes provide a scaffold that is required for the organization of extracellular lipids into lamellar membranes (59, 60).

Treatment of cultured keratinocytes and topical treatment of normal mouse skin with activators of PPARα, PPARβ/δ, and PPARγ increase the mRNA and protein levels of markers of keratinocyte differentiation, such as involucrin, filaggrin, loricrin, and transglutaminase-1 (33, 43, 49, 53, 61–67). Experiments using PPARα- and PPARγ-deficient mice showed that these prodifferentiating effects were specifically mediated via these receptors, because topical treatment with either PPARα or PPARγ agonists did not stimulate the increased expression of these markers of differentiation in these receptor-deficient mice (53, 62, 64). Similarly, the induction of the markers of keratinocyte differentiation by PPARβ/δ ligand was abolished in retinoid X receptor-α (RXRα)-deficient mice in vivo and in PPARβ/δ-deficient cells in vitro (43, 50). One exception was involucrin, which was inducible by PPARβ/δ ligands even in the absence of PPARβ/δ (50).

Likewise, treatment of cultured keratinocytes and normal mouse skin with LXR agonists also stimulated an increase in involucrin, loricrin, filaggrin, and transglutaminase-1 mRNA and protein levels (35, 68). In LXRβ-deficient mice (note that LXRβ is the predominant LXR isoform expressed in murine epidermis), oxysterol treatment did not increase the expression of these differentiation markers, again indicating that these effects are receptor-mediated (35). Either deletion or mutation of one distal AP-1 binding site (2117 to −2111 bp) in the involucrin promoter abolished the oxysterol-responsiveness in vitro (68). Treatment of cultured human keratinocytes transfected with an AP-1 response element-luciferase construct with LXR activators demonstrated an increase in luciferase activity, indicating that LXR activators increase AP-1 binding (68). Moreover, increased AP-1 DNA binding was observed in nuclear extracts isolated from 22(*R*)-hydroxycholesterol-treated cultured human keratinocytes (i.e., increased gel shift) (68). Supershift analysis in oxysterol-treated cultured human keratinocytes further revealed that Fra-1 and jun-D were the predominant proteins in the AP-1 complex in these cells (with a marked Fra-1 increase) (69). Although the supershift experiment showed that Fra-1 and jun-D were increased, other AP-1 factors may not be detected by this technique. Therefore, we also assessed alterations in the individual components of the keratinocyte AP-1 complex by Western and Northern blot analysis. Treatment with oxysterols increased the protein and mRNA levels of Fra-1 and jun-D and also moderately increased c-Fos (69). In contrast, the protein and mRNA levels of Fra-2, Fos-B, jun-B, and c-Jun did not change. These results show that treatment of primary cultured human keratinocytes with 22(*R*)-hydroxycholesterol increased the protein levels of Fra-1, jun-D, and c-fos. Therefore, we hypothesize that the LXR activator-mediated increase in involucrin gene expression is attributable to an increase in the binding of AP-1 factors (69). It should be



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noted that similar to the involucrin promoter, the promoter region of many of the other genes that increase during keratinocyte differentiation (e.g., loricrin and transglutaminase-1) also have AP-1 binding sites and that their expression is known to be stimulated by increased AP-1 binding (70–72). Thus, an increase in AP-1 binding could be a general mechanism by which LXR activation concurrently increases the expression of many genes required for keratinocyte differentiation.

The mechanism by which PPAR activation increases the expression of the keratinocyte genes important in differentiation is unknown, but it is also likely to be mediated by increases in AP-1 activity. Studies have shown that deletions or mutations in the distal AP-1 site of the involucrin promoter also abolished the ability of PPARα agonists to increase involucrin expression (62, 64). Additionally, studies have implicated Notch and STAT5a signaling upstream of PPARγ-induced keratinocyte differentiation (73, 74). Together, these data demonstrate that activation of all three PPAR isoforms and LXR results in increased keratinocyte differentiation and that these effects are receptor-mediated in the epidermis.

## PPAR AND LXR ACTIVATION IMPROVES PERMEABILITY BARRIER FUNCTION

Topical treatment of normal mouse skin with PPAR and LXR activators does not affect basal transepidermal water loss (i.e., permeability barrier function is not altered). However, after acute disruption of the permeability barrier by either tape-stripping or extraction of barrier lipids with repeated acetone treatment, recovery of permeability barrier function was accelerated in animals treated topically with PPAR or LXR agonists (35, 43, 53, 64, 66). There were minor differences in the effects of these agonists on permeability barrier homeostasis (e.g., whereas treatment with PPARα, PPARβ/δ, and LXR activators accelerated barrier recovery at both 3 and 6 h, PPARγ activation only accelerated barrier recovery at 6 h after either acetone treatment or tape-stripping) (53).

As discussed in detail in an earlier review in this series (75), the extracellular lipid-enriched lamellar membranes in the stratum corneum mediate the barrier to water movement. These lipid-enriched membranes are derived from the secretion of lamellar bodies by stratum granulosum cells, and the formation of the lamellar bodies by stratum granulosum cells requires three families of lipids: cholesterol, phospholipids, and glucosylceramides. After lamellar body secretion, phospholipids are converted to free fatty acids by phospholipases and the glucosylceramide is catabolyzed to ceramides by β-glucocerebrosidase in the stratum corneum extracellular space. Thus, the extracellular lipid bilayers are generated and maintained by a complex pathway with four key steps: *1*) epidermal lipid synthesis; *2*) lamellar body formation; *3*) lamellar body secretion; and *4*) extracellular processing of precursor lipids to the lipids that form the extracellular lipid membranes. Studies have shown that PPAR and LXR agonists activate all of these key steps.

### Lipid synthesis

In mice, topical treatment with PPARα, PPARβ/δ, PPARγ, and LXR activators increased cholesterol, fatty acid, and sphingolipid synthesis in the epidermis (76). This increase can most likely be attributed to increased mRNA expression of the corresponding enzymes of cholesterol, fatty acid, and ceramide biosynthesis that were shown to be induced in mouse skin and in human organotypic skin cultures (77, 78). Specifically, increased expression was observed for serine-palmitoyltransferase, long-chain acyl-CoA synthase, acyl-CoA oxidase, ceramide glucose synthase, and HMG-CoA synthase in human organotypic skin cultures treated with a PPARα activator (78). In mouse skin treated with a PPARβ/δ activator, HMG-CoA synthase 2 was reported to be induced (77). Very strong induction of sphingolipid synthesis was observed after PPARβ/δ activation, and topical PPARβ/δ activation dramatically increased barrier-specific ceramide species (76). In contrast, PPARγ activation did not exert significant effects on sphingolipid synthesis. Overall, PPARγ activation appeared to have the least effect on epidermal lipid synthesis among the PPAR and LXR activators tested (53).

### Lamellar body formation

ABCA12 is a member of the ABC superfamily that facilitates the delivery of sphingolipids to lamellar bodies in keratinocytes (79). This is a key step in the formation of lamellar bodies, and the absence of ABCA12 results in a diminished number of lamellar bodies and lamellar bodies with an abnormal structure (79). Recently, gene mutations in ABCA12 were found to underlie harlequin ichthyosis and lamellar ichthyosis, two devastating skin disorders (80, 81). Both PPARγ and PPARβ/δ activators markedly stimulate ABCA12 mRNA expression in human keratinocyte in a dose- and time-dependent manner (82). Increased ABCA12 mRNA levels were accompanied by an increase in ABCA12 protein. LXR activators also increased ABCA12 mRNA levels in keratinocytes, but to a lesser extent. In contrast, activators of PPARα did not alter ABCA12 expression (82). These results demonstrate that PPAR and LXR activators increase ABCA12 expression, which would facilitate the formation of lamellar bodies.

### Lamellar body secretion

In mice topically treated with activators of PPARα, PPARβ/δ, and LXR, but not PPARγ, there was accelerated lamellar body secretion both in the basal state and after barrier disruption (76). Interestingly, whereas in control animals, almost all lamellar bodies are secreted from the apical surface of cells at the stratum granulosum-stratum corneum interface, in PPARα, PPARβ/δ, and LXR activator-treated animals, secretion of lamellar bodies occurs between nucleated cells several layers beneath the interface ("premature" secretion) (76). Notably, a requirement of PPARβ/δ, but not of PPARα and PPARγ, for



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lamellar body formation and secretion has been shown in receptor-deficient mouse models (51, 77). Moreover, mice with genetic ablation of RXRα or RXRα/β show a lamellar body defect identical to PPARβ/δ knockout mice, and strikingly, topical PPARβ/δ activation corrected the lamellar body defect in the epidermis of RXR-deficient mice (77). Together, these results suggest that PPARβ/δ is the key PPAR isoform involved in lamellar body formation and secretion.

### Extracellular processing of precursor lipids

Lamellar bodies deliver lipids to the extracellular space (see above). In addition, they also secrete a family of lipid-processing enzymes, including β-glucocerebrosidase, required for the extracellular processing of glucosylceramides to ceramides in the stratum corneum, an essential step in the formation of mature, functional lamellar membranes (75, 83). Topical treatment of mouse epidermis with PPAR and LXR activators increased the activity of β-glucocerebrosidase (76). The increase in activity was shown both by fluorescence assay using epidermal extracts in vitro and in vivo by in situ zymography. Increased enzyme activity was localized to the outer epidermis, where processing of the extracellular lipid into mature membrane structures occurs. Similarly, treatment of human organotypic skin cultures with a PPARα activator resulted in increased β-glucocerebrosidase, but not steroid sulfatase and sphingomyelinase, mRNA expression (78).

Thus, PPAR and LXR activators could improve permeability barrier homeostasis by affecting a number of the key steps required for the formation of the extracellular lamellar membranes that mediate the permeability barrier.

## OTHER EFFECTS OF PPAR AND LXR ON LIPID METABOLISM IN THE EPIDERMIS

### Lipid storage

PPARβ/δ activation has been shown in keratinocytes to induce proteins that are important for lipid storage, including fasting adipocyte factor and adipocyte differentiation protein (43). This induction by PPARβ/δ activation correlated with the intracellular accumulation of lipid droplets in treated keratinocytes that predominantly contained triglycerides (43). This increase in adipocyte differentiation protein was specific for PPARβ/δ, because the increase did not occur in PPARβ/δ-deficient keratinocytes (49). Whether activators of other PPAR isoforms or LXR have similar effects on lipid storage in keratinocytes has not yet been determined.

### Cholesterol sulfate synthesis

Cholesterol sulfotransferase type 2B isoform 1b (SULT2B1b) is a key enzyme in the synthesis of cholesterol sulfate, a critical regulator of keratinocyte differentiation and desquamation, as well as a mediator of barrier homeostasis (84, 85). PPAR and LXR activators increased SULT2B1b mRNA levels in keratinocytes independently of their differentiation stage, with the most dramatic effect (a 26-fold increase) induced by the PPARγ activator ciglitazone (86). Additionally, cholesterol sulfotransferase activity was also increased. Ciglitazone increased SULT2B1b mRNA in a dose- and time-dependent manner. The increase in SULT2B1b mRNA levels by ciglitazone appeared to occur at the transcriptional level, because the degradation of SULT2B1b was not accelerated by ciglitazone (86). In addition, cycloheximide almost completely blocked the ciglitazone-induced increase in SULT2B1b mRNA levels, suggesting that the transcription of SULT2B1b mRNA is dependent on new protein synthesis (86). Thus, LXR and PPAR activators regulate the expression of SULT2B1b, the key enzyme in the synthesis of cholesterol sulfate, which is a potent regulator of epidermal differentiation and corneocyte desquamation.

### ABCA1

ABCA1 is a membrane transporter that mediates cholesterol efflux from cells and thus plays an important role in regulating cellular cholesterol levels. ABCA1 is expressed in human keratinocytes and murine epidermis, and LXR activation markedly increases ABCA1 mRNA and protein levels in keratinocytes and mouse epidermis (87). In addition, activators of PPARα and PPARβ/δ, but not PPARγ, also increase ABCA1 expression in human keratinocytes (87).

## PPAR AND LXR ACTIVATION COULD COORDINATELY REGULATE STRATUM CORNEUM FORMATION

The formation of a normal stratum corneum requires both corneocytes and the extracellular lipid matrix. Traditionally, the formation of these two components was viewed as concurrent but independent processes. However, as lipids accumulate within the keratinocyte for the formation of lamellar bodies, it is possible that these lipids or metabolites of these lipids will activate PPAR and LXR, which could then stimulate the expression of the proteins required for keratinocyte differentiation. In addition, as described above, the activation of PPAR and LXR would also increase epidermal lipid synthesis, lamellar body formation (by increasing ABCA12 expression), lamellar body secretion, and the enzymes required for the metabolism of precursor lipids to those present in the lamellar membranes. Hence, the increase in lipids that occurs during keratinocyte differentiation to facilitate lamellar body formation could activate PPAR and LXR, thereby serving as a signal that could coordinately regulate the formation of the stratum corneum by stimulating both the formation of corneocytes and the extracellular lipid matrix (**Fig. 1**).

## ROLE OF PPAR AND LXR IN EPIDERMAL ONTOGENESIS

Using both an in vitro skin explant model and in vivo experiments (administration into the amniotic fluid), we



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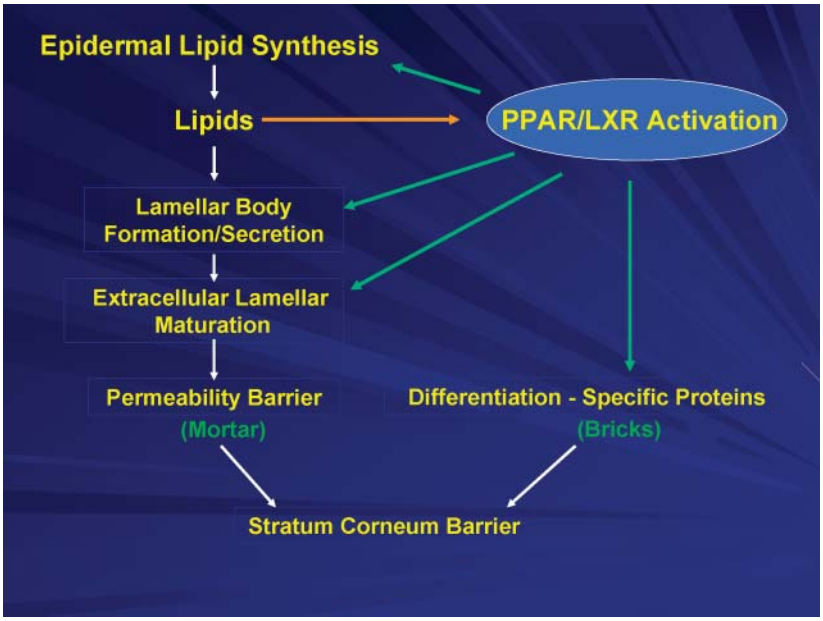


**Fig. 1.** Proposed role for peroxisome proliferator-activated receptor/liver X receptor (PPAR/LXR) in stratum corneum formation.

have shown that compounds that activate PPARα and LXR accelerate fetal epidermal development (34, 88). The formation of the extracellular lipid membranes that mediate barrier function and the development of the permeability barrier are accelerated by activators of PPARα and LXR (34, 88). In parallel, the activities of two key enzymes, β-glucocerebrosidase and steroid sulfatase, that are required for lipid processing in the stratum corneum are stimulated by PPARα and LXR activators (34, 88). In addition, PPARα and LXR activators accelerate the formation of mature corneocytes (34, 88). The expression of involucrin, loricrin, and filaggrin increases, and this increase occurs earlier in gestation than in controls (34, 88). Moreover, PPARα knockout mice display a delay in epidermal differentiation and stratum corneum formation (89). Together, the stimulation of both the cellular (bricks) and extracellular (mortar) components of the stratum corneum by PPARα and LXR activators results in the generation of a mature, functionally competent stratum corneum earlier in fetal development. In contrast to studies with PPARα and LXR activators, the PPARγ activators troglitazone and prostaglandin J2 as well as activators of other nuclear hormone receptors, such as the vitamin D receptor and the retinoic acid receptor, did not accelerate fetal epidermal development (88). Studies are currently in progress to examine the effect of PPARβ/δ activators on fetal epidermal development.

## EFFECTS OF PPAR AND LXR ACTIVATION ON EPIDERMAL PROLIFERATION AND CELL DEATH

The differential effects of PPAR and LXR activation on various cellular functions are summarized in **Tables 1, 2**. Results from experiments assessing the effects of PPAR and LXR activation on cellular proliferation and cell death have varied depending on the experimental context. First, pharmacologic PPARα activation decreased keratinocyte proliferation both in vitro and in vivo (61, 64). Moreover, in a mouse model of epidermal hyperproliferation induced by repeated barrier disruption to the flank skin of hairless mice (90), topical PPARα activation inhibited proliferation and increased keratinocyte apoptosis [number of terminal uridine deoxynucleotidyl transferase (TUNEL)-positive cells] (91). Additionally, transgenic mice that overexpress PPARα in the epidermis have demonstrated less epidermal hyperplasia in response to TPA, and keratinocytes from these animals proliferated

TABLE 1. Effects of PPAR/LXR activation

| Receptor | Inflammation | Epidermal Differentiation | Barrier Function | Skin Ontogenesis | Epidermal Proliferation |
|---|---|---|---|---|---|
| PPARα | ↓ | ↑ | ↑ | ↑ | ↓ |
| PPARγ | ↓ | ↑ | ↑ | No effect | ↓ |
| PPARβ/δ | ↓ | ↑ | ↑ | Not determined | ↓ |
| LXR | ↓ | ↑ | ↑ | ↑ | ↓ |

LXR, liver X receptor; PPAR, peroxisome proliferator-activated receptor.



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TABLE 2. Consequences of genetic PPAR/LXR ablation

| Receptor | Inflammation | Epidermal Differentiation | Barrier Function | Skin Ontogenesis | Epidermal Proliferation |
|---|---|---|---|---|---|
| PPARα | ↑ | Slight ↓ | No effect | ↓ | No effect |
| PPARγ | No effect | No effect | No effect | Not determined | ↑ |
| PPARβ/δ | ↑ | ? Our data show increase | ↓ | Not determined | ↑ |
| LXR | Not determined | Slight ↓ | No effect | Not determined | ↓ |

more slowly in culture (92). In contrast to the above results demonstrating a role for PPARα in regulating keratinocyte proliferation, mice deficient in PPARα displayed only thinning of the stratum granulosum, but not altered epidermal thickness or proliferation (64, 89, 93, 94). These results indicate that the activation of PPARα in the epidermis decreases keratinocyte proliferation but that the absence of PPARα does not have major effects on keratinocyte proliferation, presumably because of the redundant effects of other PPAR isoforms or other factors that regulate keratinocyte proliferation and thereby compensate for the absence of PPARα (Tables 1, 2).

PPARβ/δ activators have antiproliferative effects on keratinocytes in vitro (33, 95–98), but topical application of PPARβ/δ activators to normal mouse skin in vivo did not affect proliferation (43). Additionally, the frequency and distribution of TUNEL-positive keratinocytes was not changed by topical treatment of mice with PPARβ/δ activators. In contrast, mice deficient in PPARβ/δ have a thickened epidermis with both increased keratinocyte proliferation and increased cell death (51, 99), indicating that the PPARβ/δ effects on proliferation outweigh those on cell death. In addition, PPARβ/δ-deficient mice displayed an exaggerated hyperproliferative response to TPA, suggesting that this receptor is critical for attenuating epidermal proliferation (30, 52). It was suggested that in the hyperproliferative epidermis of psoriatic skin, PPARβ/δ overexpression mediates keratinocyte proliferation via NF-κB (44). Together, these results indicate that the absence of PPARβ/δ leads to increased keratinocyte proliferation and that under some experimental conditions PPARβ/δ activators inhibit keratinocyte proliferation. Finally, downstream signaling of PPARβ/δ via the PKBα/Akt1 kinase pathway was shown to protect keratinocytes from cell death (99), which is reviewed in detail elsewhere (16, 17).

PPARγ activators exert antiproliferative effects on cultured keratinocytes in vitro (9, 100, 101). After topical application of PPARγ activators to normal mouse skin, there is an increase in both keratinocyte proliferation and keratinocyte cell death, with the net result being no change in epidermal thickness (53). However, in mice with epidermal hyperproliferation secondary to repeated barrier disruption, PPARγ activators have marked antiproliferative effects (102). Thus, the proliferative state of the keratinocytes may determine the effect of PPARγ activation on keratinocyte proliferation. In situations in which there is rapid keratinocyte proliferation, PPARγ activators may be antiproliferative.

Topical treatment of normal mice with oxysterol ligands of LXR resulted in a decrease in epidermal thickness and keratinocyte proliferation (proliferating cell nuclear antigen staining) and increased cell death (TUNEL staining) (35). Furthermore, treatment of hyperproliferative epidermis with oxysterols restored epidermal homeostasis (i.e., decreased hyperproliferation and stimulated differentiation), resulting in a return of epidermal thickness toward normal (35). Because mouse skin predominantly expresses LXRβ, these studies demonstrated that oxysterols, acting via LXRβ, can inhibit proliferation. Finally, in LXRβ and LXRα/β double deficient mice, thinning of the epidermis was observed (35). The latter was an unexpected finding given the decrease in epidermal thickness and keratinocyte proliferation with oxysterol treatment. The mechanism underlying this observation remains to be elucidated.

The effects of PPAR and LXR activation on keratinocyte proliferation could have implications regarding epithelial carcinogenesis, and that issue is discussed below.

## ROLE OF PPAR IN SKIN CANCER

As discussed above, studies have shown that PPAR activation modulates keratinocyte proliferation. Moreover, several studies have suggested that PPAR activation could interfere with carcinogenesis in the skin. Initially, it was reported that mice whose skin was chronically exposed to chemical carcinogens were less susceptible to carcinogenesis when fed a PPARα activator (103). Subsequently, pharmacologic activation of PPARγ was reported to inhibit carcinogenesis in mouse epidermis (104–106). Next, PPARβ/δ- and PPARγ-deficient mice were shown to be more susceptible to chemically induced carcinogenesis (chronic application of phorbol esters to the epidermis) (97). Protein kinase C-α phosphorylation and protein kinase C-α ubiquitination were increased in TPA-treated cells from these animals, indicating a role of the protein kinase C-α/mitogen-activated protein kinase/extracellular signal-regulated protein kinase pathway in attenuating cell proliferation in response to PPARβ/δ (97). The effects of pharmacological PPARβ/δ activation on skin carcinogenesis have not yet been determined, but it should be noted that in premalignant actinic keratoses as well as in overt squamous cell carcinoma, increased PPARβ/δ expression has been observed (107, 108).

In addition to nonmelanoma skin cancer, there have been reports of a possible role of PPARs in malignant melanoma (i.e., PPARγ activation was reported to inhibit the proliferation of human melanoma and melanocyte cell lines) (38, 109). A recent report, however, evaluating the putative risk of genetic polymorphisms in the PPARγ gene for the development of malignant mela-



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noma has yielded inconsistent results in two independent case-control studies (110). The lack of replication in independent patient cohorts makes a causal relationship between polymorphisms in PPARγ as a major risk factor for malignant melanoma unlikely, but it remains to be seen whether these polymorphisms instead contribute to disease progression or influence the response to treatment. A mouse model assessing growth of inoculated melanoma cells showed tumor growth retardation in PPARβ/δ-deficient mice, which was attributed to hyperplastic, but abnormally organized vascularization (111). Finally, PPARγ activation has been shown to induce apoptosis in (non-epidermal) cutaneous lymphoma cell lines (112).

To the best of our knowledge, the role of LXR in skin cancer has not yet been studied.

## CLINICAL TRIALS IN HUMANS

Alterations in PPAR expression in psoriasis (32, 44) and the anti-inflammatory and prodifferentiating effects of PPAR and LXR activation on the epidermis described above prompted clinical trials exploring the efficacy and safety of PPAR-targeted therapy. A striking improvement of skin lesions had initially been documented in patients with psoriasis treated with the oral PPARγ activator troglitazone (9, 113). Although subsequent clinical trials using the oral PPARγ activator rosiglitazone did not substantiate the initial troglitazone observation (114), favorable effects of oral pioglitazone not only on psoriatic skin lesions (10, 115) but also on psoriatic arthritis (8) have been reported. An ongoing phase II trial is currently evaluating the efficacy and safety of a combination of pioglitazone with acitretin in psoriasis (NCT00395941: clinicaltrials.gov). In contrast, topical treatment of psoriatic skin with the PPAR activators etradecylthioacetic acid and rosiglitazone were not efficacious (116–118). With regard to atopic dermatitis, a recent abstract indicates that topical treatment with a PPARα activator has beneficial effects (119). Despite the animal data described above implicating PPAR activation as a promising approach for inhibiting or treating skin cancer, no reports from studies in humans have been published. Similarly, studies of the effect of LXR activators on skin disease in humans also have not been reported.

## CONCLUSIONS

The epidermis is an active site of lipid metabolism, and PPAR and LXR provide a platform to sense these lipids to coordinate downstream events and to regulate a variety of cellular functions. Our knowledge about PPAR and LXR in skin physiology and pathology has evolved rapidly in recent years. Not only do they have robust anti-inflammatory activity in skin, but they also modulate epidermal proliferation, carcinogenesis, differentiation, and permeability barrier function, which identifies them as promising drug targets for the treatment of skin disease.

These studies were supported by National Institutes of Health Grants AR-39448, AR-050629, AR-049932, and HD-29706, by the Medical Research Service, Department of Veterans Affairs, by University of Innsbruck Grant M55, and by Austrian Science Fund Grants J1901-MED, J2112-MED, and P16990-B05.

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