

Functions of Peroxisome Proliferator-Activated Receptors (PPAR) in Skin Homeostasis

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ABSTRACT: The peroxisome proliferator-activated receptors (PPAR) are ligand-activated transcription factors that belong to the nuclear hormone receptor family. Three isotypes (PPAR α , PPAR β or δ , and PPAR γ) with distinct tissue distributions and cellular functions have been found in vertebrates. All three PPAR isotypes are expressed in rodent and human skin. They were initially investigated for a possible function in the establishment of the permeability barrier in skin because of their known function in lipid metabolism in other cell types. *In vitro* studies using specific PPAR agonists and *in vivo* gene disruption approaches in mice indeed suggest an important contribution of PPAR α in the formation of the epidermal barrier and in sebocyte differentiation. The PPAR γ isotype plays a role in stimulating sebocyte development and lipogenesis, but does not appear to contribute to epidermal tissue differentiation. The third isotype, PPAR β , regulates the late stages of sebaceous cell differentiation, and is the most effective isotype in stimulating lipid production in these cells, both in rodents and in humans. In addition, PPAR β activation has pro-differentiating effects in keratinocytes under normal and inflammatory conditions. Finally, preliminary studies also point to a potential role of PPAR in hair follicle growth and in melanocyte differentiation. By their diverse biological effects on cell proliferation and differentiation in the skin, PPAR agonists or antagonists may offer interesting opportunities for the treatment of various skin disorders characterized by inflammation, cell hyperproliferation, and aberrant differentiation.

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Peroxisome proliferator-activated receptors (PPAR) belong, together with the receptors for thyroid hormones, retinoids, steroid hormones, and vitamin D, to the nuclear hormone receptor family. They require heterodimerization with the retinoid X receptors (RXR, NR2B) for binding to DNA as ligand-activated transcription factors that regulate the expression of target genes containing peroxisome proliferator response elements (PPRE) in their promoters. The PPAR subfamily consists of three isotypes, which are named PPAR α (NR1C1), PPAR β or δ (NR1C2), and PPAR γ (NR1C3). Each isoform is characterized by a distinct tissue distribution and

specific functions (1). PPAR α has a main function in FA catabolism in the liver, and regulates amino acid metabolism, urea synthesis, and inflammatory responses (1,2). PPAR γ plays a pivotal role in adipocyte differentiation and then in maintenance of the differentiated state, as well as in lipid storage. Furthermore, like PPAR α , it has been implicated in the downregulation of multiple inflammatory processes (1,2). PPAR β is the most ubiquitously expressed isotype, but little is known about its functions, mainly because of the lack, until recently, of selective PPAR β agonists. Nevertheless, recent studies have suggested a role for PPAR β in embryonic development, colon tumorigenesis, skin wound healing, fat catabolism, and oligodendrocyte differentiation (3,4).

Specific roles for PPAR in vertebrate development have emerged from both *in vitro* and *in vivo* models, in particular during the differentiation of adipose tissue, brain, and placenta in mice (5). The importance of PPAR in lipid metabolism in various cell types has led to the investigation of PPAR expression and function during the differentiation of skin, which is a tissue with high rates of FA and cholesterol metabolism largely devoted to the formation of the epidermal permeability barrier. During skin development, several nuclear hormone receptors, including the estrogen, thyroid, androgen, and retinoid receptors, and their respective ligands have been implicated in the ontogeny of the epidermal barrier, hair follicle growth, and skin homeostasis (6,7).

In this review, we will summarize the PPAR functions recently identified in skin homeostasis, including epidermal barrier formation, hair follicle growth, sebocyte differentiation, and melanogenesis.

MAIN FUNCTIONS OF PPAR α AND PPAR β IN THE HEALTHY AND INJURED EPIDERMIS

The epidermis is renewed continuously and its integrity is dependent on a tightly regulated balance between cell proliferation, differentiation, and apoptosis. During its maturation, which happens mainly in the latest stages of fetal development, the epidermis evolves from a single layer of epithelial cells (periderm) to a fully stratified and differentiated epithelium (Fig. 1). This process involves the sequential expression of structural proteins (keratins, involucrin, loricrin, and filaggrin) and synthesis of specific lipids (sphingolipids, FFA, and cholesterol). The outermost layer of the epidermis, the stratum corneum, is the end product of keratinocyte differentiation and consists of a layer of cross-linked proteins and lipids,

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Abbreviations: ADRP, adipose differentiation-related protein; E, embryonic day; FIAF, fasting-induced adipose factor; PPAR, peroxisome proliferator-activated receptor; PPRE, peroxisome proliferator response element; RXR, retinoid X receptor; TNF, tumor necrosis factor; TPA, tetradecanoylphorbol acetate.

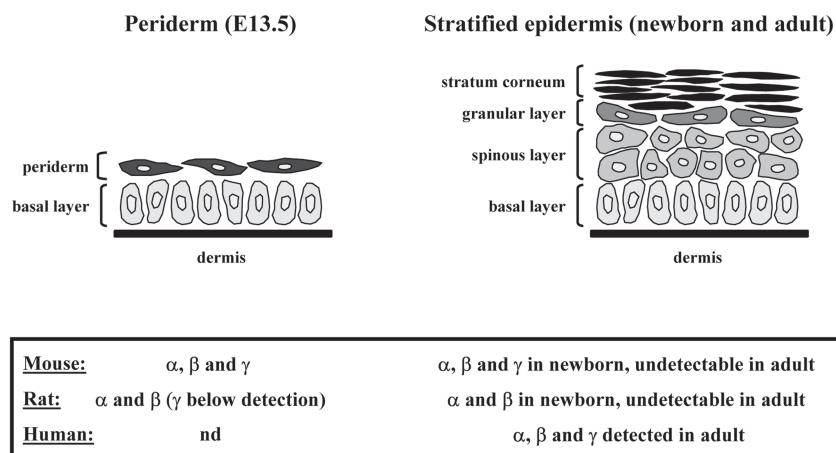


FIG. 1. Schematic representation of interfollicular epidermis development. During late fetal development (between embryonic day E13.5 and the end of gestation) in mouse skin, the epidermis changes from a single basal undifferentiated layer (basal layer) covered by a transient superficial layer of cells (periderm), to a fully stratified and differentiated epithelium, with sequential formation of suprabasal layers (spinous and granular layers). The end product of differentiation resides on the surface of the epidermis (stratum corneum) and provides the main permeability barrier of the skin. Expression patterns of PPAR α (α), PPAR β (β), and PPAR γ (γ) determined or not (nd) during mouse (3) and rat (8,9) epidermal development, and in human adult interfollicular epidermis (10,11), are summarized in the bottom panel.

which functions as a barrier to transepidermal water loss and as a defense against physical damage, microbes, and xenobiotics.

During mouse and rat embryonic development, all three PPAR isotypes, and predominantly PPAR β , have been detected in the interfollicular epidermis from embryonic day 13.5 (E13.5) onward (3,8). Interestingly, PPAR expression is associated with all major events of the fetal maturation of the epidermal barrier. After birth, PPAR gradually disappear from the interfollicular epidermis to become undetectable in the adult animals (Fig. 1) (3,9). In contrast, the three PPAR isotypes are highly expressed in the basal and suprabasal layers of human adult interfollicular epidermis (Fig. 1), with PPAR β being again the predominant subtype (10,11). Consistent with the expression pattern of PPAR in the developing rodent skin, several reports have concentrated on the involvement of PPAR in processes such as cell proliferation, differentiation, and permeability barrier development (see Table 1). A variety of PPAR α activators, including clofibrate, were shown to accelerate the morphologic and functional maturation of the epidermal permeability barrier in fetal rat skin both *in vitro* and *in vivo* (12–14). This is evidenced by decreased transepidermal water loss, increased epidermal stratification, and increased expression of the two specific late keratinocyte differentiation markers, loricrin and filaggrin. PPAR α ligands also inhibit epidermal proliferation and induce keratinocyte differentiation in adult mouse epidermis *in vivo* (15,16). Furthermore, these activators restore epidermal homeostasis in murine models of hyperproliferative epidermis (17). In contrast, the two PPAR γ ligands, troglitazone and prostaglandin J2, did not affect the development of barrier function or epidermal morphology in fetal rat skin (12), and no specific function in skin maturation

has been attributed so far to this isotype (Table 1). In favor of a potential role of PPAR β in epidermal differentiation in rodents, the pan PPAR(α/β) activator linoleic acid (18) was shown to accelerate epidermal barrier development in fetal rat skin explants (12). In addition, an important role of PPAR β in mediating keratinocyte differentiation induced by inflammation was demonstrated in mouse primary keratinocytes (19). Importantly, the PPAR β -selective agonist GW1514 stimulated mouse epidermal differentiation without affecting cell proliferation *in vivo*, by inducing the expression of the late differentiation markers filaggrin and loricrin (20). Also, topical treatment of mice with GW1514 accelerates the restoration of permeability barrier functions after disruption by tape stripping, solvent, or detergent treatment (20), in support of the importance of the pro-differentiating effect of PPAR β activation.

Novel information on the role of PPAR in epidermis homeostasis also came from PPAR mutant mouse models. Although normal skin architecture was initially reported in PPAR α -knockout mice (5,21), these animals show delayed fetal skin development between E18.5 and birth, with defects in the formation of the stratum corneum (22). Morphologic analysis of adult PPAR α -null epidermis revealed a thinned stratum granulosum, with focal parakeratosis, indicative of impaired keratinocyte differentiation (15). Thus, consistent with its expression pattern, PPAR α might be important for the maturation of the epidermis during late embryogenesis, but dispensable for normal renewal of the epidermis in the adult animals. Interestingly, PPAR α also regulates the early inflammation phase during skin wound healing, as the recruitment of immune cells to the wound site is impaired in PPAR α -null mice (3). PPAR γ heterozygous mice, or PPAR γ -null mice born after placental rescue, show no defect in

TABLE 1
Effects of Peroxisome Proliferator-Activated Receptor Agonists in Various Cell Types of the Skin^a

Cell types		Rodents	Human
Keratinocytes	α	↗ differentiation <i>in vitro</i> (WY; CLO; OA) (12;14;17) and <i>in vivo</i> (WY; CLO) (13;15)	↗ differentiation (WY; CLO; OA) (15;30;31)
		↘ proliferation <i>in vivo</i> (WY; CLO) (15;17)	↗ lipid accumulation (WY) (20;30)
	β	↗ differentiation <i>in vitro</i> (LD; LA) (12;19) and <i>in vivo</i> (GW) (20) No effect on proliferation <i>in vivo</i> (GW) (20)	↗ proliferation (WY; CLO) (10;31) ↗ differentiation (LD; GW; TTA) (10;20) ↗ lipid accumulation (GW) (20)
	γ	No significant effect on differentiation <i>in vitro</i> (TRO; PGJ2) (12)	No effect on proliferation (LD) (10) No effect on differentiation (BRL; PGJ2) (10;31) ↘ proliferation (TRO; BRL) (10;33)
Hair follicles and melanocytes	α	nd	↗ survival of cultured hair follicles (CLO) (34) ↘ proliferation and ↗ melanogenesis in melanocytes (WY) (42)
	β	nd	No effect on proliferation and melanogenesis in melanocytes (BEZ) (42)
	γ	nd	↘ proliferation and ↗ melanogenesis in melanocytes (CIG) (42)
Sebocytes	α	↗ differentiation (WY) (36;37;39) No effect on proliferation (WY) (39)	No effect on differentiation (WY) (38)
	β	↗ differentiation (LA; PGI2) (36;37;39) ↗ proliferation (PGI2) (39)	↗ differentiation (LA) (38)
	γ	↗ differentiation (TRO; BRL) (36;37;39) No effect on proliferation (TRO) (39)	No effect on differentiation (CIG) (38)

^aThis table summarizes the stimulatory (↗) or inhibitory (↘) effects of treatment with PPAR α (α), PPAR β (β), and PPAR γ (γ) agonists on the differentiation and proliferation in various cell types derived from rat and mouse (Rodents) as well as human (Human) skin. These results were obtained in *in vitro* studies, except in rodent keratinocytes where both *in vitro* and *in vivo* experiments were performed. Effects of PPAR ligands on the differentiation of hair follicles and melanocytes in rodents have not been determined (nd). PPAR agonists used in each study are indicated as follows: BEZ, bezafibrate; BRL, BRL-49653; CIG, ciglitazone; CLO, clofibrate; GW, GW1514; LA, linoleic acid; LD, L-165041; OA, oleic acid; PGI2, carbaprostacyclin; PGJ2, 15-deoxy-prostaglandin J2; TRO, troglitazone; TTA, tetradecylthioacetic acid; WY, Wy-14,643.

epidermal maturation (3,23). In addition, PPAR γ -null cells are able to participate in the formation of the epidermal tissue in PPAR γ -null and wild-type chimeric mice, suggesting very little or no contribution of PPAR γ in this process (24). Analysis of PPAR β -mutant skin reveals no defect in fetal and adult epidermal architecture, or in the expression of keratinocyte differentiation markers (3). However, epidermal hyperplasia in response to tetradecanoylphorbol acetate (TPA) treatment was enhanced in PPAR β -mutant animals, emphasizing the role for PPAR β in the control of keratinocyte proliferation and differentiation (3,25). Similarly, the slightly increased keratinocyte proliferation index in PPAR β heterozygous animals is also in favor of the existence of such a control (3). Consistent with these observations, PPAR β expression is rapidly upregulated following challenges that stimulate keratinocyte proliferation, such as hair plucking or cutaneous injury, and skin wound healing is altered in PPAR β -mutant mice (3), largely due to a disrupted balance between proliferation and apoptosis (19,26), as well as to defects in keratinocyte adhesion and migration (3,27).

Important roles of PPAR α and PPAR β in human keratinocyte differentiation were also reported (see Table 1). As already mentioned, PPAR β is the predominant isotype in these keratinocytes (10,11,28,29). Its expression remains high and unchanged during the differentiation of cultured keratinocytes, or during the stratification and keratinization of the epidermis in *in vitro* reconstructed skin (10,28), whereas it increases upon squamous differentiation in human tracheobronchial epithelial cells (29). PPAR α and PPAR γ are expressed at lower levels, but their expression increases upon keratinocyte

differentiation in similar models (10,28). In human keratinocytes, PPAR β - (L-165041 and GW1514) and PPAR α (clofibrate and Wy-14,643)-selective agonists induce the expression of a number of epidermal differentiation markers, including involucrin (10,20,30), whereas PPAR γ ligands (BRL-49653 and prostaglandin J2) have no effect (10,31). The hypothesis that PPAR may also affect the metabolism of lipids in keratinocytes is supported by the observation that PPAR α ligand Wy-14,643 increased both the synthesis of cer-amides and cholesterol derivatives in a human skin equivalent model (30). Also, the PPAR β selective agonist GW1514 increases TG accumulation and induces the adipose differentiation-related protein (ADRP) and fasting-induced adipose factor (FIAF) expression in human keratinocytes, two proteins that have potential important roles in lipid metabolism (20).

IMPLICATION OF PPAR IN HYPERPROLIFERATIVE SKIN DISEASES

Based on their diverse biological effects on keratinocyte proliferation and differentiation, PPAR ligands may become interesting compounds for the treatment of various epidermal disorders characterized by inflammation, keratinocyte hyperproliferation, and aberrant differentiation, such as psoriasis. In support of an involvement of PPAR in psoriatic epidermis, PPAR β expression was reported to be dramatically increased in the hyperproliferative lesional skin from psoriatic patients (11,28), probably as a response to pro-inflammatory signals in the lesions. It is indeed well established that PPAR β gene

expression is upregulated in mouse skin in response to inflammatory cytokines, such as tumor necrosis factor alpha (TNF- α) (19). In addition, putative PPAR β ligands, such as lipoxygenase products, are generated at high levels in psoriatic skin lesions, and may therefore activate the increased amount of PPAR β (11). The fact that PPAR β is probably naturally highly active in the psoriatic lesions may explain why the PPAR β agonist tetradecylthioacetic acid has no strong anti-psoriatic effect when applied topically (32). By contrast to PPAR β expression, no or little change in the cutaneous levels of PPAR α and PPAR γ was observed in lesional psoriatic skin (11,28), and the PPAR α (clofibrate) and PPAR γ (rosiglitazone) agonists had no effect when applied on psoriasis plaques (32). Nevertheless, it is encouraging to note that treatment with the synthetic PPAR γ agonist troglitazone was reported to normalize the histological characteristics of psoriatic skin in organ culture, and to reduce the epidermal hyperplasia of psoriasis in the severe combined immunodeficient mouse and human skin transplant model of psoriasis (33). Finally, two PPAR α ligands (Wy-14,643 and clofibrate) were able to restore epidermal homeostasis in subacute and chronic models

of hyperproliferative epidermis in hairless mice (17), even though these models do not perfectly mimic psoriatic or other human disorders. Obviously, further *in vivo* and clinical studies are needed to better define the potentially beneficial roles of PPAR in this pathology.

ROLE OF PPARS IN HAIR FOLLICLE AND SEBOCYTE DIFFERENTIATION

Skin epithelial progenitor cells give rise to the epidermis, as well as to the epithelial component of skin appendages, including hair follicles and their associated sebaceous glands. Hair follicle morphogenesis is governed by complex bidirectional interactions between epithelial keratinocytes and the underlying dermal cells of the mesenchymal condensations (Fig. 2). These interactions control a tight balance between keratinocyte proliferation and apoptosis. In rodents, all three PPAR isotypes are expressed in the differentiating hair follicles from the early embryonic developmental stages (Fig. 2). PPAR remain highly expressed in postnatal and adult hair follicles, whereas they disappear from the interfollicular epider-

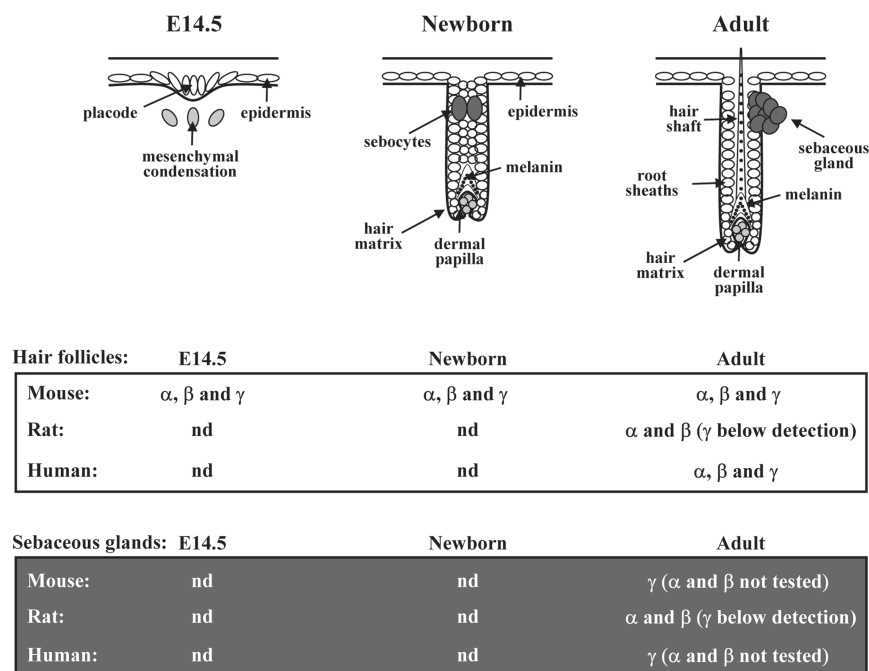


FIG. 2. Schematic representation of murine hair follicle morphogenesis. Hair follicle development occurs between embryonic day 14.5 (E14.5) and postnatal day 7 (P7) in mouse, and is governed by bidirectional epithelial–mesenchymal interactions between epithelial keratinocytes and dermal fibroblasts of underlying mesenchymal condensations. Following dermal induction, hair follicle precursors appear first as thickening of the uniform epithelial surface (placode, E14.5). Follicular epithelial cells will next proliferate, followed by downgrowth into the dermis, leading to the elongation of hair follicles (Newborn), and will finally differentiate into the typical structures of mature hair follicles, including root sheaths, hair matrix, and hair shaft (Adult) (46). In parallel, melanin starts to be produced in the precortex region, and the first sebocytes form the sebaceous gland (Newborn). Expression patterns of PPAR α (α), PPAR β (β), and PPAR γ (γ) determined or not (nd) in mouse (8), rat (10), and human (35) hair follicles at indicated stages, as well as in mature sebaceous glands (8,28,39), are given in the bottom panels.

mis after birth (3,8), as already mentioned (see Figs. 1, 2). A detailed analysis of the expression of PPAR in human hair follicles shows that they are specifically located in both epithelial and dermal hair follicle cells (34). In addition, the PPAR α ligand clofibrate was reported to increase the survival of human hair follicles *in vitro*, within a narrow range of concentrations (Table 1) (34). Although a possible function of the two other PPAR isotypes in hair follicle growth has not yet been examined, it is interesting to note that conditional ablation in the murine epidermis of RXR α , the most abundant heterodimeric partner of PPARs in keratinocytes, results in delayed hair follicle maturation and alopecia (35).

Chronologically, the latest differentiated cell type to appear in the developing follicle is the oil-rich sebocytes. They arise from cells within the superficial hair follicle and will eventually form a gland located outside the hair follicle. Sebaceous lipogenesis, leading to the accumulation of lipid droplets and finally to sebum excretion, represents a major step in the differentiation process and differentiated state of sebaceous gland cells. Rodent and human sebocytes were shown to express the three PPAR, either in cell culture or *in vivo* (Fig. 2), the predominant isotype being PPAR β (9,24,36–38). Consistently, and in addition to androgens that are well known to regulate the growth and maturation of sebocytes, PPAR agonists and retinoids were recently found to affect sebaceous gland differentiation (see Table 1). Activation of PPAR γ and PPAR α by respective selective agonists has no effect on sebocyte growth (39), but stimulates lipid droplet accumulation in cultured rat preputial sebocytes, as assessed histochemically using Oil Red O staining (36,37). This effect was not observed in epidermal cells (37) or in cultured human sebocytes (38), possibly due to the different selective PPAR agonists or to various ligand concentrations used in each study. In parallel, RXR selective ligands have prominent differentiative and weak proliferative effects on sebocytes (40). The RXR α selective retinoid CD2809 also amplified the pro-differentiative effect of PPAR in preputial sebocytes, suggesting a cooperation between PPAR and RXR agonists in promoting differentiation of these cells (39). In both rat and human cultured sebocytes, the pan PPAR(α/β) activators carbaprostacyclin and linoleic acid were more effective than PPAR α or PPAR γ agonists in stimulating sebocyte lipid droplet formation, suggesting an important contribution of PPAR β in this process (37–39). Interestingly, PPAR β seems more important in the late stages of sebocyte differentiation (37,38), whereas it was involved in the early adipocyte differentiation (41), suggesting that it plays different roles in the differentiation program of each cell type.

It is noteworthy that, in spite of the relative importance of PPAR in lipid metabolism and their high expression in sebocytes, in neither PPAR α nor PPAR β mutant mouse models has sebaceous gland function been closely examined so far. In contrast, inactivation of the PPAR γ gene has underscored a crucial contribution of PPAR γ in sebocyte differentiation, although it appears dispensable for epidermal differentiation.

Indeed, and as already discussed, chimeric mice for PPAR γ -null and wild-type cells showed little or no contribution of mutant cells to the development of sebaceous glands, suggesting that PPAR γ -null cells cannot develop into sebocytes (24).

NEW PUTATIVE FUNCTION OF PPARS IN MELANOCYTE DIFFERENTIATION

The pigment-producing cells of the skin are called melanocytes and their activity is the major determinant of the color of the hair and skin. Melanocytes originate from the neural crest and migrate to the basal layer of the epidermis and the hair matrix during embryogenesis. Interestingly, all three PPAR were detected in cultured human melanocytes (42) and in melanoma cells (43). Consistent with the role of PPAR agonists in cellular proliferation and differentiation in keratinocytes, PPAR α (Wy-14,643) and PPAR γ (ciglitazone) ligands were shown to inhibit the proliferation and to stimulate the melanin synthesis of cultured melanocytes (Table 1), whereas bezafibrate, a preferential activator for PPAR β in *Xenopus* (44), had no effect on melanin content (42). In agreement with this study, several PPAR γ agonists, including troglitazone and rosiglitazone, were previously demonstrated to inhibit cell growth in human malignant melanoma (43), and topical application of retinoic acid was shown to improve hyperpigmented skin lesions such as melasma (45). Because of their antiproliferative and prodifferentiative effect on melanocytes, it is tempting to suggest that PPAR and RXR ligands may be beneficial in the treatment of melanomas. However, too little is known in this context for the moment, and further investigation is needed.

DISCUSSION AND HYPOTHESIS

These studies suggest that PPAR α may contribute to sebaceous gland differentiation and epidermal permeability barrier formation by increasing both lipid metabolism and expression of structural differentiation markers, whereas PPAR γ plays a unique role in stimulating sebocyte function. Furthermore, PPAR β was identified as the predominant isotype in the skin, and as a modulator of cell differentiation in both keratinocytes and sebocytes.

Because of their diverse biological activities in epidermal processes such as keratinocyte proliferation and differentiation, PPAR may represent a major research target for the understanding and treatment of many skin diseases resulting in disturbance of normal tissue homeostasis and epidermal hyperproliferation, such as benign epidermal tumors, papillomas, melanomas, and psoriasis. In addition, due to the increasing number of studies implicating PPAR in the control of sebocyte differentiation, the development of PPAR antagonists that can interfere selectively with sebum production may constitute an important element in the prevention of acne vulgaris, characterized by excess sebum production.

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