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Peroxisome Proliferator-Activated Receptors and their Ligands

Entry Into the Post-Glucocorticoid Era of Skin Treatment?

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Abstract

Glucocorticoids have remained one of the most frequently used classes of drugs for the treatment of skin diseases since their introduction more than 50 years ago. As a result of the discovery of new members of the nuclear hormone receptor (NR) superfamily, alternative therapeutic interventions that target retinoid and vitamin D receptors have been developed. Peroxisome proliferator-activated receptors (PPARs) comprise another important NR subfamily, consisting of three different isotypes: PPARα, PPARδ (PPARβ) and PPARγ. These NRs are activated by a variety of natural and synthetic ligands such as fatty acids, eicosanoids, and antidiabetic and antihyperlipidaemic agents. While these receptors are established as regulators of gene expression in lipid and glucose homeostasis, evidence is now accumulating that PPARs also play a crucial role in cutaneous biology. Results from *in vitro* and *in vivo* studies have indicated the involvement of PPARs in epidermal maturation, proliferation and differentiation, as well as in immune and inflammatory responses, carcinogenesis, hyperpigmentation and skin wound healing. Furthermore, treatment of psoriatic patients with PPARγ activators (thiazolidinediones) has been shown to induce beneficial effects. However, the effects of PPAR ligands should be carefully evaluated to determine whether they are in fact mediated via PPAR-dependent mechanisms. Nonetheless, PPARs seem to have significant potential as therapeutic targets in skin inflammatory disorders.

Glucocorticoids were, and still are, the first-line agents in dermatological therapy of non-infectious inflammatory skin diseases. However, despite their clinical use for more than 50 years, the application of these drugs is often restricted by various adverse events. General strategies to improve current treatment options encompass not only the development of more potent glucocorticoids with fewer unwanted effects[1] but also the development of new vehicles for topical delivery of glucocorticoids.[2] However, glucocorticoids with an ideal benefit : risk profile have not yet been discovered.[1,3] Glucocorticoids bind to receptors that belong to the superfamily of ligand-regulated nuclear hormone receptors (NRs), which includes the retinoic acid receptor, the vitamin D receptor, the thyroid hormone receptor and the peroxisome proliferator-activated receptor (PPAR). NRs control a variety of physiological processes, the dysfunction of which may lead to life-threatening diseases, including cancer, diabetes mel-

litus, hyperlipidaemia, arteriosclerosis and cholestasis. Furthermore, various dermatological diseases appear to be associated with NRs because of the role these receptors play in keratinocyte differentiation and proliferation, and their immunomodulatory properties.

Over the last decade, new aspects of the function and signalling mechanisms of PPARs have been revealed, thus, PPARs have come to provide a potential target for innovative therapeutic agents. Ligands for PPARs have already been introduced into the market as antidiabetic and antihyperlipidaemic agents, and more agents are currently under evaluation in clinical trials for these diseases. In this article we critically summarise recent developments in this field, focussing on new therapeutic options for inflammatory skin disorders, hyperpigmentation, skin cancer and wound healing.

1. Nuclear Hormone Receptors

NRs are ligand-dependent transcription regulators that are involved in diverse physiological functions such as cell growth, differentiation, metabolism and development, as well as the preservation of cellular homeostasis. To date, approximately 50 different NRs have been identified in the human genome. In accordance with their mechanism of interaction with their DNA response elements (hormone response elements), NRs are divided into two subtypes. Following ligand binding, type I receptors bind their associated DNA sequences as monomers and homodimers; this group of receptors includes the classical steroid hormone receptors, that is, the receptors for glucocorticoids, estrogens, progestogens, androgens and mineralocorticoids. Type II receptors, for example the thyroid hormone receptor, retinoic acid receptor, vitamin D receptor, liver X receptor, pregnane X receptor and PPAR, primarily interact with their target genes as heterodimers with the retinoid X receptor (RXR). For some NRs, the corresponding ligands still await identification; therefore, these receptors are referred to as orphan nuclear receptors and are categorised into a type III class.

NRs share a common structure with four major domains: an N-terminal region (A/B domain), a DNA-binding domain (DBD) [C domain], a hinge region (D domain) and a ligand-binding domain (LBD) [E/F domain]. The amino terminus has a variable transactivation domain, termed activation function 1, that is cell and promoter specific and that is recognised by transcription factors. The central DBD is highly conserved within the NR superfamily and contains two zinc-finger motifs. The hinge region allows conformational changes in the molecule. The carboxy-terminal LBD is well conserved between the various family members; however, there is sufficient divergence to guarantee selective ligand recognition. This domain also contains the ligand-induced activation function, which is crucially involved in transcriptional coregulator interaction. Recruitment of proteins, called coregulators, mediates the effects of NRs on transcription.[4,5] Coregulators influence the transcriptional activity of NRs either positively (coactivators) or negatively (corepressors) at different functional stages. These proteins occur in multiple complexes, harbour multiple enzymatic activities and link receptors to chromatin or to the basal transcription machinery.

2. Peroxisome Proliferator-Activated Receptors (PPARs)

PPARs were originally described as molecular targets of peroxisome proliferators, a large group of compounds that includes herbicides, plasticisers and antihyperlipidaemic chemicals. Shortly thereafter, it was shown that PPARs respond to endogenous fatty acids and control a variety of target genes involved in lipid and glucose metabolism. To date, three PPAR isoforms have been identified in mammalian cells; these have been designated as PPARα,[6] PPARδ (also known as PPARβ)[7] and PPARγ.[8] In mice and humans, two distinct N-terminal isoforms of PPARγ (termed PPARγ1 and PPARγ2) have been found.[9] According to the unified nomenclature system, PPARs are termed NR1C1 (PPARα), NR1C2 (PPARδ) and NR1C3 (PPARγ).[10] Binding as heterodimers with RXRs to specific PPAR response elements (PPREs) in the promoter regions of specif-

ic target genes regulates gene expression. In the absence of a ligand, the PPAR-RXR heterodimer and nuclear receptor corepressor proteins form high-affinity complexes that inhibit binding of the nuclear receptor heterodimer to the promoter and, thus, transcriptional activation. Binding of the ligand to the heterodimer causes the corepressor to be released from the complex, leading to binding of the activated heterodimer to the response element, which in turn results in either the suppression or activation of target genes.

2.1 PPAR Ligands

PPAR ligands can be classified into synthetic peroxisome proliferators, antihyperlipidaemic, insulin-sensitising and anti-inflammatory compounds, or the constituents of naturally occurring medium- and long-chain fatty acid, eicosanoid ligands. Naturally occurring PPAR agonists are low-affinity ligands which activate specific receptor isoforms when present at micromolar levels. Despite a relatively high sequence homology of PPAR subtypes, LBDs allow certain ligand specificity for each subtype. In fact, site-directed mutagenesis of the LBD crystal structures has shown that mutation of a single amino acid affects the subtype selectivity of several chemical classes of ligands.[11] Nonetheless, many established PPAR ligands show only modest selectivity with respect to a particular PPAR isotype, despite extensive research during the last few years to identify more potent and selective PPAR ligands.[12-15] Furthermore, next-generation PPAR modulators, including dual agonists, pan agonists and partial antagonists, are currently being evaluated for the treatment of metabolic disorders in several clinical studies.

PPARα binds various ligands, including leukotrienes, prostaglandins, plasticisers and synthetic drugs (e.g. WY 14643 and fibric acid derivatives [fibrates]). A search for physiological ligands revealed that PPARα is activated by a variety of long-chain fatty acids and, in particular, polyunsaturated fatty acids (PUFAs), such as docosahexaenoic acid, linoleic acid, linolenic acid, palmitic acid, oleic acid and arachidonic acid.[16-18] While leukotriene B_4 (LTB_4) and the PUFA metabolite 8(S)-hydroxyeicosatetraenoic acid (HETE) selectively activate PPARα,[19,20] fibrates and WY 14643 activate PPARγ in addition to PPARα. Bezafibrate does not exhibit strong selectivity for any of the three PPAR subtypes.

PPARβ/δ is activated by saturated and unsaturated fatty acids,[18,21] eicosanoids, including prostaglandin (PG)A_1 and PGD_2, and a biologically stable synthetic prostacyclin agonist. Therefore, prostacyclins may be endogenous PPARδ agonists.[22] To date, only a few potent and selective ligands for PPARδ have been identified, such as the phenoxyacetic acid derivates GW 501516 and L 165041.[23,24]

PUFAs, eicosanoids and prostaglandins are weak activators of PPARγ (figure 1). Furthermore, metabolites of arachidonic acid, such as 15-deoxy-Δ12,14-PGJ_2 (15d-PGJ_2) and 15(S)-HETE, as well as oxidised metabolites of linoleic acid, for example 9-hydroxyoctadecadienoic acid (9-HODE) and 13-HODE present in oxidised low-density lipoproteins, have been shown to activate PPARγ.[25-27] Synthetic ligands for PPARγ are the antidiabetic thiazolidinediones (also known as glitazones)[26,28] and several NSAIDs including indomethacin, fenoprofen, ibuprofen and flufenamic acid.[29] With classical full PPARγ agonists, such as the thiazolidinediones, bodyweight gain and peripheral oedema are often observed. Several partial PPARγ agonists have been developed that demonstrate similar or even better insulin-sensitising effects than the thiazolidinediones, but with less adipogenic activity.[13,30,31] This effect has been linked to the recruitment of a different set of cofactors compared with those activated by full agonists.

2.2 PPAR Expression in Human and Murine Skin

All three PPAR subtypes have been identified in most mammalian tissues, although their relative expression varies considerably. In human skin, all PPAR subtypes are expressed in the adult interfollicular epidermis, with PPARδ being by far the most abundantly expressed PPAR subtype in this tis-

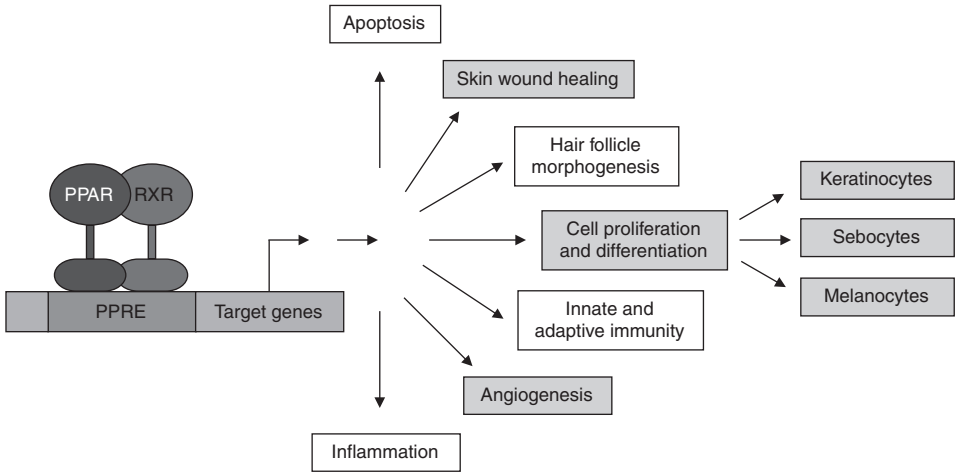

Fig. 1. After heterodimerisation with retinoid X receptor (RXR) peroxisome proliferator-activated receptors (PPARs) control gene expression by binding to DNA sequences, termed peroxisome proliferator response elements (PPRE), in the promoter region of target genes. Principal functions of PPARs in the skin are illustrated.

sue.[32-34] PPARα and PPARγ are found at much lower levels in the skin and their expression has been reported to increase upon differentiation, whereas PPARδ expression remains high during the differentiation of human keratinocytes. In addition to PPAR expression in keratinocytes, all three PPAR isoforms have been found in human sebocytes, melanocytes, dermal and epidermal hair follicle cells, and PPARγ has been found in normal human skin fibroblasts.[35-38] Analysis of PPAR expression in the hyperproliferative psoriatic epidermis and psoriatic lesions revealed that both PPARα and PPARγ expression is decreased, while PPARδ expression is upregulated.[33,39] A similar expression pattern has been found in lesions from human non-melanoma skin cancers.[40] Immunohistochemical investigations of actinic keratosis and squamous cell carcinoma lesions have demonstrated reduced immunoreactivity for PPARα and increased PPARδ expression levels compared with the normal skin of each individual. No difference in immunoreactivity was noted for PPARγ.

PPARs have also been detected in rat and mouse epidermis.[32,41-44] All isotypes are expressed during embryonic epidermal development, starting before stratification and differentiation of the murine epidermis, and continuing in the early postnatal stage.[44] In the adult interfollicular epidermis, PPARs are below detection levels, whereas they remain expressed in the hair follicles. PPARα and PPARδ are upregulated in the interfollicular epidermis of mice during wound healing or proliferation induced by topical application of 12-O-tetradecanoyl-phorbol-13-acetate (TPA).

2.3 PPAR Knockout Mice

PPAR knockout mice provide a valuable tool for the elucidation of the role of PPARs in cellular events. PPAR null and PPAR heterozygous mice display no major skin abnormalities,[44-49] although knockout of the *PPAR*γ gene is an embryonic-lethal event that results in mice dying *in utero* around gestational day 10.[46] PPARα null mice display reduced longevity and more severe and frequent age-dependent lesions, particularly in the liver, kidney and heart.[50] The incidence of skin lesions as a cause of death was slightly more frequent in null mice than in wild-type mice. However, these skin lesions have not been investigated histologically. Stratum corneum formation *in utero* is delayed in PPARα knockout mice,[51] and a transient and initial delay in wound healing has also been reported.[44] Moreover, morphological analysis of the adult epidermis exhibits a thinned stratum granulosum with

decreased keratohyalin granules, focal parakeratosis and a slight decrease in the expression of keratinocyte differentiation markers.[52] For PPARδ null mice, a delay during the whole healing process, postponing its completion by 2–3 days, was demonstrated.[44] Recently, skin-specific PPAR knockout mice have been generated using the LoxP-Cre site-specific recombination strategy; these mice show normal skin differentiation, have a normal skin barrier and have a normal TPA response, except for a slight epidermal hyperplasia.[49]

3. PPARs in the Pathogenesis of Dermatological Diseases

Since classical NRs such as the retinoic acid and vitamin D receptors regulate most of the relevant signalling pathways in epidermal cells, retinoids and vitamin D analogues have gained widespread use in the treatment of epidermal disorders. Recently, evidence has been accumulating that suggests that PPARs might be promising targets for drug treatment of skin disorders such as psoriasis, acne, atopic dermatitis and contact dermatitis. Figure 1 illustrates principal functions of PPARs in the skin.

3.1 Psoriasis

Psoriasis is characterised by abnormal proliferation and differentiation of epidermal keratinocytes, as well as dermal infiltration of inflammatory components. Although a variety of local and systemic therapies are available for the treatment of psoriasis, including ligands for the NRs (such as corticosteroids, retinoids and vitamin D analogues), current treatments are often restricted because of their adverse effects. Thus, novel therapeutic interventions with improved benefit : risk ratios are eagerly awaited.

Hanley et al.[53] were the first to show a physiological role for PPARα in epidermal homeostasis. The PPARα ligands oleic acid, linoleic acid and clofibrate accelerated the development of the stratum corneum and epidermal barrier in fetal skin explants derived from rats. In the same model, clofibrate increased the expression of profilaggrin, a major constituent of keratohyalin granules, increased the processing of profilaggrin to filaggrin, and increased the expression of loricrin, a key structural protein of the cornified envelope.[52] Furthermore, activators of PPARα induced differentiation in human keratinocyte cultures, as indicated by increased protein and messenger (mRNA) levels of two differentiation-specific proteins: involucrin and transglutaminase. Similar to other inducers of differentiation, such as vitamin D derivates and retinoic acid, clofibrate inhibited keratinocyte growth and proliferation *in vitro* and *in vivo*.[54,55] Intra-amniotic administration of clofibrate or linoleic acid accelerated the maturation of the stratum corneum and epidermal barrier in fetal rats.[43] Notably, PPARδ and PPARγ activators had no effect on rat epidermal maturation *in vitro* and *in utero*. Topical treatment of hyperproliferative epidermis in adult mice with PPARα activators restored epidermal homeostasis and increased apoptosis,[56] and 8(S)-HETE induced differentiation as indicated by increased keratin-1 expression in murine keratinocyte cultures.[57] In living skin equivalents, WY 14643 strongly influenced epidermal lipid metabolism and enhanced the synthesis of membrane coating granules, which are secreted into the extracellular space and constitute the structural components of the epidermal permeability barrier.[58]

Regarding PPARδ, activators of the NR stimulate differentiation in cultured human keratinocytes[34,59] and *in vivo* after topical application to normal and hyperproliferative mouse skin.[59] Furthermore, overexpression of PPARδ induced differentiation in cultured keratinocytes and protected against cell death *in vitro*.[60,61] The PPARδ-selective ligand L 165041 induced expression of involucrin and transglutaminase and, interestingly, simultaneous addition of the PPARγ-selective ligand rosiglitazone resulted in a strong synergistic induction of involucrin.[34] Administration of tetradecylthioacetic acid (TTA), a potent pan PPAR agonist, resulted in a strong upregulation of the expression of involucrin and transglutaminase and a dramatic decrease in proliferation, whereas L 165041 showed no antiproliferative effects.[34] In accordance, PPARδ activators did not inhibit keratinocyte

proliferation *in vivo*.[59] This is in contrast with other studies reporting inhibition of keratinocyte proliferation.[48,62] PPARδ-deficient mice exhibited an exacerbated hyperplastic response to topical application of TPA on the skin, suggesting that lack of PPARδ influences control of keratinocyte proliferation and/or differentiation.[48] Using the highly specific PPARδ ligand GW 0742 and a PPARδ-null mouse model, previous observations on induction of keratinocyte differentiation have been confirmed.[62] However, a dose-dependent inhibition of cell proliferation was observed in response to GW 0742 in wild-type cells, whereas no effect was seen in keratinocytes derived from PPARδ-null mice.

Differential effects on keratinocyte differentiation and proliferation have also been reported for PPARγ. Previous studies have demonstrated that PPARγ may not be involved in the epidermal differentiation process.[34,53,54] A recent study demonstrated that activators of PPARγ stimulated epidermal differentiation both *in vitro*, using cultured human keratinocytes, and *in vivo*, when applied topically to mouse skin, while no effect was observed in mice lacking PPARγ in the epidermis.[49] However, since skin-specific PPAR knockout mice show normal skin differentiation, PPARγ does not appear to be crucial for mouse skin function and development. Although PPARα, PPARδ and PPARγ activators seem to stimulate keratinocyte differentiation, there are differences in the proliferative effects of the PPAR ligands. Specifically, activation of PPARα has been shown to inhibit keratinocyte proliferation, leading to a decrease in epidermal thickness.[55] In contrast, topical treatment with activators of PPARδ and PPARγ did not result in epidermal thinning.[49,59] However, several studies observed inhibition of epidermal proliferation upon challenge with PPARγ activators. Troglitazone inhibited the proliferation of both normal and psoriatic human keratinocytes, stabilised the histological characteristics of psoriatic skin in organ culture and reduced the epidermal hyperplasia of psoriasis in the severe combined immunodeficient mouse as well as in human skin transplant models of psoriasis.[63] In keratinocytes and human skin in organ culture, rosiglitazone reduced keratinocyte proliferation and motility, and production of matrix metalloproteinases-1 and -9; these effects were not observed in dermal fibroblasts.[64] Novel thiazolidinedione derivatives synthesised by linking the antioxidant vitamin thioctic acid (α-lipoic acid) to benzoxy-troglitazone were shown to be potent activators of PPARγ and modest activators of PPARα.[65] Two compounds, designated BP 1003 and BP 1017, inhibited proliferation of human keratinocytes more potently than rosiglitazone. The specific effects of PPARs on keratinocyte proliferation and differentiation are illustrated in figure 2a.

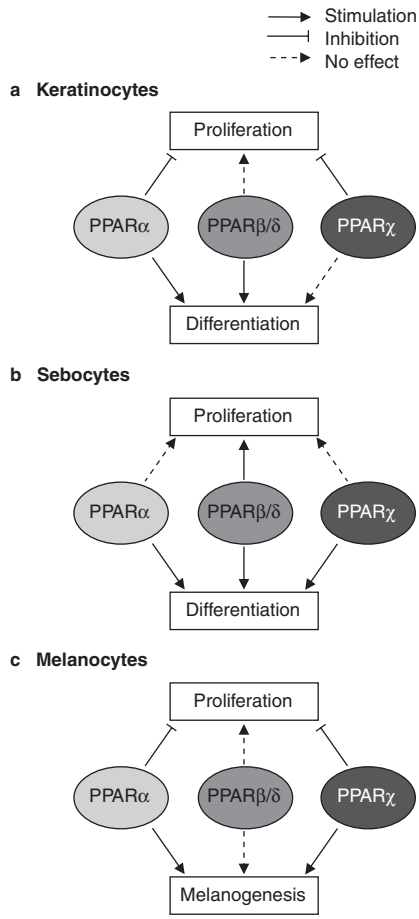

Fig. 2. Effects of peroxisome proliferator-activated receptor (PPAR)-α, PPARδ and PPARγ on the differentiation and proliferation in (**a**) keratinocytes, (**b**) sebocytes and (**c**) melanocytes.

Another signalling system that has been proposed to participate in the regulation of early keratinocyte differentiation is the transmembrane receptor Notch-1 and its peptide ligand Delta-1. Interestingly, the Notch ligand jagged-1 induced IκB kinase α (IKKα)-mediated nuclear factor-κB (NF-κB) activation, increased PPARγ expression and triggered complete differentiation in keratinocyte monolayers.[66]

Evidence has accumulated that psoriasis is a prototypic T helper (T_h)-1-associated autoimmune disease, which may be improved by immune deviation of polarised T_h1 responses into anti-inflammatory T_h2 responses.[67] Activation of PPARγ in T cells and dendritic cells has been shown to inhibit the production of cytokines that are important for T_h1 differentiation.[68,69] Taken together, although conflicting data have been published, ligand activation of PPARs might be a novel approach to selectively induce differentiation and inhibit cell proliferation, thus representing a new molecular target for the treatment of psoriasis.

3.2 Acne

Acne is a chronic inflammatory condition of the pilosebaceous unit that primarily affects adolescents and young adults. The different types of acne, such as comedonal, papulo-pustular and nodular acne, reflect a multifactorial pathophysiological process that includes follicular hyperkeratinisation, hypersecretion of sebum, colonisation by the anaerobic diphtheroid *Propionibacterium acnes* and, consecutively, the release of inflammatory mediators into the follicle and surrounding dermis. Since PPARs are regulators of lipogenesis during adipocyte differentiation, their involvement in sebocyte differentiation has been proposed (figure 2b).

Linoleic acid and, to a lesser extent, WY 14643 and other PPAR agonists, initiate differentiation of immature cultured rat preputial sebocytes and cultured human SZ95 sebocytes.[35,70,71] Sebocyte differentiation has been induced using cognate ligand agonists of either PPARs[71] or RXRs,[72] and augmentation of sebocyte differentiation was expected, and in fact proven to occur, following costimulation using the specific RXR ligand CD 2809.[73] Although the RXR ligand and the PPARδ/α ligand carbaprostacyclin ($cPGI_2$) have each been shown to enhance proliferation significantly, no further increase in growth was observed when the two compounds were applied together, indicating that proliferation does not seem to be mediated by the interaction of PPAR and RXR.[73]

Androgens and PPAR ligands both stimulate sebaceous lipid synthesis.[70] Treatment of human sebocytes with arachidonic acid and linoleic acid induced lipogenesis, as demonstrated by cell enlargement, accumulation of lipid droplets in the cytoplasm and nuclear fragmentation, all phenomena that are observed during terminal sebocyte differentiation.[74,75] In a pilot clinical study, treatment with the 5-lipoxygenase inhibitor zileuton, which inhibits the synthesis of LTB_4 from arachidonic acid, significantly reduced the synthesis of sebaceous lipids and the formation of acne lesions.[76] However, it has recently been reported that fatty acids including linoleic acid, linolenic acid, oleic acid and arachidonic acid, among other PPARα and PPARγ ligands, inhibit sebaceous lipogenesis in human chest sebaceous glands after 7-day organ maintenance, whereas bezafibrate, clofibrate, LTB_4 and PGJ_2 were ineffective.[77] The reason for this discrepancy is not clear, although it may be due to the use of different *in vitro* models. The organ-maintained sebaceous gland may preserve a greater degree of differentiation than the primary culture, as speculated by the authors. In addition, it has been suggested that fatty acid effects on sebocyte differentiation might only be partially dependent on PPARs.[71]

Nonetheless, PPAR ligands seem to be involved in the regulation of lipid metabolism in human sebaceous glands. Since suppression of sebum secretion is associated with reduced acne activity, these findings may provide new directions for the development of acne treatments.

3.3 Atopic Dermatitis, Contact Dermatitis and Photodermatitis

Recent evidence has indicated a crucial role for PPARs in the control of inflammatory responses. Both PPARα and PPARγ have been shown to negatively regulate the inflammatory process and to play a role within the immune system, via actions on macrophages, B and T lymphocytes, dendritic cells, mast cells and eosinophils.[78]

The anti-inflammatory and immunomodulatory properties appear to arise mainly through the capability of PPARs to antagonise several important signalling cascades by transrepressing transcription factors such as NF-κB and activator protein 1 (AP1). Recently, PPARδ has also been implicated in the control of inflammation during skin wound healing.[60]

Initially, it was demonstrated that PPARα is capable of reducing the duration of a LTB_4- or arachidonic acid-induced inflammatory response and of impairing the wound healing process during the inflammatory phase.[19] Activation of PPARα inhibited the expression of the proinflammatory cytokines interleukin (IL)-6 and IL-8 after UVB stimulation *in vitro*, and topical application of WY 14643 increased the minimal erythema-inducing dose in UVB-irradiated human skin. Furthermore, UVB irradiation resulted in downregulation of all three PPAR subtypes. Notably, the UVB-mediated decrease was partially compensated for by pre-treatment with WY 14643.[79] Hence, the downregulation of PPARs by UVB irradiation might explain exaggerated and prolonged inflammation. Recently, UVB irradiation of keratinocytes has also been associated with PPARγ agonistic activity.[80] In two different mouse models of cutaneous inflammation, the anti-inflammatory effects of PPARα ligands were investigated. Employment of topical TPA served as a model of irritant-mediated contact dermatitis and topical oxazolone acted as model of allergic contact dermatitis.[81] In both models, topical application of clofibrate, WY 14643 or linoleic acid decreased ear thickness and weight similar to the potent corticosteroid clobetasol, whereas no significant change was observed in mice deficient for PPARα. Furthermore, clofibrate reduced tumour necrosis factor (TNF)-α and IL-1α staining in the epidermis. Naturally occurring palmitoylethanolamide (PEA) has recently been shown to selectively induce gene expression of PPARα upon topical administration.[82] In the animal models, PEA reduced oedema formation in wild-type, but not PPARα knockout, mice.

In a model of irritant contact dermatitis, the selective PPARδ agonist, GW 1514, exerted anti-inflammatory effects that were comparable with those of clobetasol.[59] Moreover, the thioctic acid-based PPARγ activators, BP 1003 and BP 1017, inhibited IL-2 production by activated peripheral lymphocytes. However, only the water-soluble derivative, BP 1017, displayed anti-inflammatory effects when administered either orally or topically in a mouse model of allergic contact dermatitis.[65] The anti-inflammatory effects of PPARδ agonists add to the delayed wound healing described in section 3.6.

The influence of two PPARγ activators, GW 9578 and ciglitazone, on immunoglobulin (Ig) production has been investigated *in vitro* and *in vivo*.[83] In peripheral blood mononuclear cells characterised by high spontaneous basal IgE production from both nonallergic individuals and patients with atopic dermatitis, both agents inhibited IgE production. Ciglitazone also inhibited the production of cytokines, such as IL-4 and IL-6, which are known to promote IgE synthesis. Moreover, IL-4-mediated immune responses in ovalbumin-sensitised mice declined following ciglitazone treatment. Topical ciglitazone or troglitazone application reduced the cutaneous inflammatory response induced by TPA or oxazolone in hairless mice.[49] However, since this effect was also observed in mouse skin that was deficient for PPARγ, the inhibition of cutaneous inflammation was independent of PPARγ. Previous studies with an identical mouse model have demonstrated that PPARα and PPARδ agonists mediate their anti-inflammatory effects directly via either PPAR subtype.[59,81] Another member of the NR family has recently been associated with anti-inflammatory activity. Topical application of liver X receptor (LXR) activators suppressed

inflammation and primary cytokine production.[84] Earlier studies have demonstrated that LXR activators also stimulate epidermal differentiation, improve permeability barrier homeostasis and inhibit epidermal proliferation.[52,85,86] Overall, these data point to the potential use of PPAR activators as novel NSAIDs in the topical treatment of inflammatory skin diseases.

3.4 Skin Carcinogenesis

The increasing prevalence of skin cancer underscores the importance of developing new therapeutic strategies to treat this disease. Given that NRs are involved in the regulation of cell growth and differentiation, PPARs may be implicated in carcinogenesis.[87] However, data published so far indicate that their role is highly complex and each PPAR isotype seems to be associated with carcinogenesis to a certain extent.

Topical application of the PPARα ligands, conjugated linoleic acid and WY 14643, moderately reduced skin tumour multiplicity in an initiation-promotion study.[88] In contrast, the PPARδ and PPARγ activators, bezafibrate and troglitazone, respectively, had no inhibitory activity, while all PPAR isoforms were upregulated in the tumour cells.

The rationale for examining the role of PPARδ in skin carcinogenesis is based on enhanced epidermal hyperplasia and mRNA levels of gene products that regulate cell cycle progression in PPARδ-null mouse skin after TPA treatment compared with wild-type controls.[48] Accordingly, topical application of TPA resulted in exacerbated epidermal hyperplasia accompanied by hyperkeratosis in PPARδ-null mice compared with controls, indicating the attenuation of epidermal cell proliferation by PPARδ. The absence of PPARδ expression reduced expression of ubiquitin C and, thus, ubiquitination of proteins induced by TPA.[89] Since protein kinases regulate cell cycle progression and apoptosis, the role of PPARδ in the mediation of the ubiquitin-dependent protein kinase C α (PKCα) and phosphorylation signalling pathways was investigated in a subsequent study.[90] After treatment with TPA, markedly higher levels of phosphorylated PKCα, mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) [MEK]1/2, and p42MAPK/ERK-2 were found in the skin of PPARδ-null mice than in TPA-treated wild-type mice. In addition, upon TPA-treatment the activity of PKCα and downstream signalling kinases was augmented, and expression of cyclo-oxygenase-2 was greater, leading to increased cell proliferation in mice lacking PPARδ. These data indicate that it may be possible that PPARδ activation could be targeted for chemoprevention of skin cancer through its ability to inhibit cell proliferation.

The expression of PPARα, PPARδ and PPARγ has been detected in melanoma cell lines, and of PPARγ in benign and malignant melanocytic lesions.[91,92] Incubation of the melanoma cell lines with specific agonists for PPARγ inhibited cell proliferation in a dose-dependent manner, whereas the PPARα agonist WY 14643 showed no effect.[92] The underlying mechanism for the antiproliferative effect of PPARγ activation has not yet been fully investigated but may be due to induction of cell cycle arrest rather than apoptosis. However, it is questionable whether these agents exert their anticancer effects directly by activation of PPARγ. In human mammary tumour cells lines, the potent and selective PPAR antagonist GW 9662 prevented activation of PPARγ but inhibited cell growth.[93] In addition, inhibition of growth induced by rosiglitazone was further enhanced in the presence of the PPARγ antagonist instead of being reversed. Notably, it has also been shown that troglitazone inhibits keratinocyte proliferation and cyclin D1 expression *in vitro* in murine skin via PPARγ-independent mechanisms.[94] Accordingly, *in vivo* studies with dietary troglitazone showed significantly reduced proliferation in keratinocytes.[95]

However, contradictory data have been obtained when the role of PPARγ in mammary, ovarian and skin carcinogenesis was studied using a mouse model of PPARγ haploinsufficiency.[96] PPARγ(+/−) mice that received 7,12-dimethylbenz[a]anthracene (DMBA) by gavage once a week for 6 weeks had a decreased survival rate and an increased number of total tumours per mouse after 25 weeks compared

with PPARγ (+/+) mice. Of the total tumours found in the skin, the individual incidences of papillomas ($p < 0.05$) and squamous cell carcinomas ($p < 0.06$) were higher among PPARγ(+/−) mice compared with their PPARγ(+/+) littermates. Thus, PPARγ(+/−) mice have increased susceptibility toward DMBA-mediated carcinogenesis, indicating a beneficial role for PPARγ-specific ligands in the prevention of skin carcinogenesis. In contrast with this study, neither topical nor dietary administration of troglitazone or rosiglitazone inhibited mouse skin carcinogenesis in either DMBA/TPA or UV carcinogenesis models.[95] The reason for the nonresponsiveness to PPARγ ligands was probably due to a very low expression of PPARγ mRNA and the lack of PPARγ in skin keratinocytes. Furthermore, it has been suggested that PPARγ may indirectly regulate the metabolism of the carcinogen DMBA into noncarcinogenic forms by cells other than keratinocytes.[96] Reduced PPARγ levels in PPARγ heterozygous mice may lead to increased levels of carcinogenic forms of DMBA in the skin, hence leading to a higher susceptibility of PPARγ heterozygous mice to DMBA-induced skin tumour development. In the DMBA/TPA-induced skin carcinogenesis model, the PPARγ ligands were applied 2 weeks after DMBA treatment.[95] The observation that PPARγ activation has no significant effect on skin carcinogenesis may be explained by the completion of DMBA metabolism and DMBA-induced damage to DNA by the time the PPARγ ligands were applied.

3.5 Hyperpigmentation

NRs such as retinoid and vitamin D receptors are involved in pigmentation. This may also hold true for the PPARs. However, while retinoic acid improves hyperpigmented skin lesions,[97] several studies have reported increased pigmentation following use of the topical vitamin D analogue calcipotriol plus phototherapy in vitiligo patients.[98,99]

In human melanocytes, mRNA expression of all three PPAR isoforms has been detected.[36] Proliferation of the melanocytes was inhibited upon stimulation with WY 14643 and ciglitazone, but not by bezafibrate, a preferential activator of PPARδ. Accompanying reduced cell growth, both PPAR agonists appeared to stimulate melanogenesis. Linoleic acid, which displays a whitening effect on hyperpigmented skin in humans, has been proven to prevent hyperpigmentary disorders, such as melasma, which are caused by dysfunction of tyrosinase, a key enzyme involved in melanin biosynthesis.[100,101] Following topical application of linoleic acid or α-linolenic acid to UV-stimulated hyperpigmented dorsal skin of brownish guinea pigs, an efficient lightening effect was be observed.[98] The pigment-lightening effects were probably caused by inhibition of melanin production in active melanocytes and enhanced desquamation of melanin pigment from the epidermis. Lately, fatty acids such as linoleic acid, but not palmitic acid, have been implicated in the regulation of pigmentation via proteasomal degradation of tyrosinase.[102]

However, the data concerning the possible role of PPARα and PPARγ in inhibition of cell growth and stimulation of melanogenesis (figure 2c) should be interpreted with caution. At present, it is unclear whether these effects are in fact regulated via PPAR-dependent mechanisms.

3.6 Wound Healing

Wound healing is a complex process encompassing a number of overlapping events, including inflammation, epithelialisation, angiogenesis and matrix deposition. Despite progress in the discovery of factors involved in wound re-epithelialisation, it still remains unclear how epidermal keratinocytes respond to the early inflammation associated with wound healing. Several studies have implicated PPARα and PPARδ in the wound healing process.[44,60,61,103-106] As mentioned in section 3.3, PPARα is involved in the early inflammatory phase during skin wound healing and exhibits a transient delay in the healing process.[44] In a recent study, transgenic mice with specific expression of a dominant negative PPARα in keratinocytes displayed a similar phenotype to PPARα null mice, indicating a major role for PPARα in keratinocytes but not in fibroblasts or immune cells.[105]

In PPARδ(+/−) mice, wound closure was markedly delayed and *in vitro* studies with cultured primary keratinocytes demonstrated a severely reduced migration rate, which may be responsible for the delayed wound healing in the heterozygous knockout animals.[44] Subsequently, it was shown that necrosis and proinflammatory cytokines, such as TNFα and interferon-γ, activate the stress-associated signalling pathway, which in turn leads to elevated *PPAR*δ gene expression via an AP1 recognition site in the PPARδ promoter.[60] Furthermore, production of PPARδ ligands triggered by TNFα resulted in increased PPARδ transcriptional activity, accelerated the differentiation of keratinocytes and increased their resistance to apoptotic signals. Finally, *in vivo* experiments with heterozygous PPARδ mutant mice demonstrated a 10-fold increase in the number of apoptotic keratinocytes at the edges of induced epidermal wounds. Protection against apoptosis may be necessary to maintain a sufficient number of viable keratinocytes at the wound edge for subsequent re-epithelialisation.

The same group demonstrated that enhanced PPARδ activity stimulates a major cellular antiapoptotic survival pathway (Akt1 pathway).[61,103] Transforming growth factor (TGF)β-1, an important cytokine produced at the wound site, was shown to inhibit inflammation-mediated induction of PPARδ via Smad3 in primary keratinocytes.[104] The antiapoptotic Akt signalling pathway seems to be involved early after injury, whereas the proapoptotic TGFβ-1pathway dominates at later stages of wound healing. *In vivo* studies revealed that genetic disruption of the *Smad3* gene or topical application of TGFβ-1 early after wound injury accelerates wound closure via a prolonged elevated expression and activity of PPARγ.[106] These studies provided novel insights into a regulatory crosstalk between TGFβ-1/Smad3 and PPARγ/Akt signalling at different stages of wound repair. Interestingly, PPARδ and Akt1 have recently been implicated in hair follicle development.[107] In follicular keratinocytes, both PPARδ and Akt1 are highly expressed during hair follicle morphogenesis and deletion of PPARδ[107] or Akt1[107,108] is associated with a significant retardation in hair follicle development.

4. Potential Clinical Use of PPARs in Psoriasis

In accordance with the observed pharmacological effects *in vitro* and *in vivo*, clinical studies have provided evidence that PPAR ligands may be effective in the treatment of psoriatic patients.

Initially, two psoriatic patients with hypertriglyceridaemia treated with oral clofibrate showed improvement of their psoriatic lesions during therapy.[109] Later, an open-label study of three diabetic patients with concomitant psoriasis suggested that troglitazone significantly improved skin lesions while inducing glycaemic control.[110] Following on from this, Ellis et al.[63] observed marked amelioration of psoriasis in two nondiabetic patients with chronic, stable plaque psoriasis after they received oral troglitazone at various dosages. However, troglitazone was withdrawn from the market in 2000 because of its association with rare but severe hepatic toxicity during antidiabetic treatment.

Recently, pioglitazone has shown beneficial effects in two pilot studies. In a double-blind, randomised, placebo-controlled, parallel-group study, 70 patients with moderate to severe plaque psoriasis received pioglitazone 15 or 30mg or placebo.[111] After treatment for 10 weeks, the efficacy was assessed by the Psoriasis Area and Severity Index (PASI). Pioglitazone was very well tolerated and was associated with a significant reduction in median PASI scores (41.1% for 15mg, 47.5% for 30mg) compared with the placebo group (21.6%). Complete clearance of lesions was observed in 40% of pioglitazone-treated patients versus 12.5% of placebo recipients. An open-label study investigated tolerability and parameters of disease activity during treatment with pioglitazone in ten patients with active psoriatic arthritis.[112] All patients received pioglitazone 30mg twice daily while continuing their current NSAID therapy. After 12 weeks, most patients showed improvement in the study endpoints. In patients with cutaneous psoriasis affecting at least 2% of their body surface, a mean percentage de-

crease in PASI of 38% was observed. The occurrence of adverse effects such as bodyweight gain and peripheral oedema seemed to be higher compared with observations in diabetes studies, which may be because of either the relatively high dose of pioglitazone or the coadministration of NSAIDs. Rosiglitazone, another antidiabetic agent of this group, is currently being investigated in phase III studies for oral treatment of psoriasis.

Approximately 75–85% of psoriatic patients are only affected in limited areas and, thus, topical drugs are often the first choice for therapeutic intervention. To date, small pilot studies have been conducted by Kuenzli and Saurat[113] to evaluate the therapeutic efficacy of topically applied PPARα, PPARδ and PPARγ activators. Topical administration of clofibrate at 0.5% twice daily over a period of 3 weeks did not improve plaque psoriasis. Similar observations have been made with TTA and rosiglitazone 0.5% applied twice daily to the lesions of patients with slight-to-moderate chronic plaque psoriasis. The treatment was well tolerated, with no skin irritation or adverse drug-related symptoms or withdrawals. After 30 days, no significant difference was observed for the reductions in the plaque PASI scores for total, scale and infiltration between the vehicle and either PPAR agonists. However, it should be noted that the drug penetration has not been evaluated and it is unclear whether the bioavailability of the drugs in the vehicle was optimal.

Genetic factors seem to play a crucial role in susceptibility to psoriasis. To date, several psoriasis susceptibility loci have been reported and linked to the development of psoriasis. Given the beneficial effects of PPARγ agonists in experimental models of psoriasis and in patients, as well as the decreased expression of PPARα and PPARγ in the lesional skin of psoriatic patients, it is interesting to speculate about a correlation between PPAR polymorphisms or gene mutations and this disease. In a recent case-control study, 192 patients with chronic plaque psoriasis and 330 healthy individuals were screened for seven genetic variations of PPARα and PPARγ.[114] However, no association between the PPAR variations and psoriasis was found.

5. PPAR-Independent Mechanisms

The studies discussed in section 4 demonstrate that the role of PPARs in cellular mechanisms is highly complex. The complexity of PPAR research further increases when it is taken into account that commonly used PPAR agonists, including eicosanoids, WY 14643, 15d-PGJ2 and troglitazone, among others, may display PPAR-independent effects on cell activation or metabolism, rendering the interpretation of the reported observations more difficult.[94,115,116] Evaluation of the effects of rosiglitazone and linoleic acid on human preadipocyte differentiation has demonstrated that the PPAR agonists may exert their effects via different biochemical pathways.[117] Furthermore, it has been reported that the involvement of PPARα in the molecular signalling of RXR activators depends on the target organ.[118] Another recent study revealed a novel mechanism for RXR homodimer signalling *in vivo*, which also has important consequences for PPARs.[119] Interestingly, RXR homodimers were found to bind selectively to functional PPREs via specific coactivator recruitment, and to induce transactivation irrespective of the presence of PPAR. It has been previously demonstrated that mice lacking functional PPARα show elevated levels of plasma free fatty acids, as well as hypoglycaemia, hypoketonaemia and hypothermia.[120] However, administration of alitretinoin (9-cis retinoic acid) 5 days before fasting enabled the mice to maintain their body temperature.[119] Thus, RXR homodimers might be able to compensate, at least in part, for the lack of function of PPARα. In addition, retinoic acid has been shown to bind PPARδ with nanomolar affinity and efficiently activates PPARδ-mediated transcription, while no activation of PPARα and PPARγ was observed.[121]

As mentioned in section 2.3, PPARγ null mice die *in utero* and, consequently, it is not yet possible to show conclusively whether all of the reported effects are actually mediated by PPARγ-dependent processes. However, studies using PPARγ heterozygous mice or mice with specific tissue PPARγ deficiencies are helpful for the evaluation of these effects. When natural or synthetic activators of PPAR

subtypes are used as the only experimental approach to evaluate the influence of PPARs on biological processes, receptor-independent effects of the chemical agents need to be considered.

6. Conclusion

Since their discovery, it has been possible to establish that PPARs have important roles in regulating various molecular and cellular mechanisms in the skin. The development of more specific and potent agonists and antagonists for each PPAR subtype may help to elucidate their signalling mechanisms and biological effects in the future. The promising results from clinical trials with thiazolidinediones in the systemic treatment of psoriasis suggest that these drugs may become an established part of the future management of psoriatic patients. Although no clinical studies with PPAR ligands for other dermatological diseases have been reported so far, ligands that mediate their effects through PPAR-dependent processes, such as linoleic acid, could also have beneficial therapeutic effects in other skin diseases such as acne, atopic and contact dermatitis, and pigmentary disorders. However, it remains to be determined whether PPARs are a suitable target for the treatment of skin diseases and, more importantly, whether their ligands show improved efficacy and fewer adverse effects than established NR ligands such as retinoids, vitamin D analogues and, particularly, glucocorticoids.

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