REVIEW

Peroxisome Proliferator-activated Receptors and their Relevance to Dermatology

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Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor superfamily and are expressed in a variety of tissues including skin and cells of the immune system. They act as ligand-dependent transcription factors which heterodimerize with retinoid X receptors to allow binding to and activation of PPAR responsive genes. Through this mechanism, PPAR ligands can control a wide range of physiological processes. Based on their effects in vitro and in vivo PPAR agonists and antagonists have the potential to become important therapeutic agents for the treatment of various skin diseases. PPARs can also be activated directly by phosphorylation to have ligand-independent effects. This review will discuss the physiology of PPARs relating this to skin pathology and their role as a target for novel therapies. Key words: psoriasis; PPARs; wound healing; thiazolidinediones; transcription factors.

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Peroxisomes are ubiquitous intracellular organelles with important roles defined in many metabolic processes (see http://www.peroxisome.org/). They derive their name from their ability to produce H$_2$O$_2$ through a group of oxidizing enzymes which use molecular oxygen to transform their substrates, releasing H$_2$O$_2$ and OH which can be toxic. The oxidative stress resulting from H$_2$O$_2$ is known to stimulate phospholipase D, which is associated with the production of phosphatidic acid and diacylglycerol. These in turn affect adenyl cyclase and protein kinase C, respectively, which can modulate a wide array of target proteins including plasma membrane receptors, contractile proteins and regulatory enzymes. As a result they have a role in many processes including cellular oxidation and respiration, lipid synthesis, metabolism and transport, sex steroid metabolism, regulation of adipose cell numbers, microsomal oxidation and ketogenesis, insulin sensitivity, as well as metabolism of a wide range of xenobiotics. There are now over 20 inherited disorders known to relate to peroxisome defects, frequently with significant cutaneous manifestations such as ichthyosis, recurrent ulceration, alopecia, follicular atrophoderma and photosensitivity, suggesting that modification of their activity may be of therapeutic benefit in the field of dermatology.
TISSUE DISTRIBUTION OF PPARs

PPARs exhibit distinct patterns of tissue distribution. PPARs are found mainly in tissues associated with high fatty acid metabolism, and thus are expressed mainly in liver, but are also found in kidney, muscle, heart, fat, B and T lymphocytes, vascular smooth muscle and at low levels in keratinocytes. Their main effect is activation of lipid catabolism but they also have a range of other effects including modulation of inflammation, wound healing and formation of the epidermal lipid barrier.

PPARβ/δ is widely expressed in most tissues but despite being the most ubiquitously expressed is perhaps the least understood. It is the dominant subtype expressed by keratinocytes in human skin. In murine epidermis, all the PPAR isotypes are expressed during fetal development but shortly after birth they become undetectable in interfollicular epidermis. Injury to skin, associated with epidermal hyperplasia, induces expression of PPARγ and PPARδ. PPARα and PPARγ seem to be important in the inflammatory phase while PPARδ is important for cell migration and re-epithelialization.

PPARγ exists in two main isofoms as a result of alternative promoter use and splicing: PPARγ1 is expressed in adipose tissue, spleen, liver, pancreas, adrenal, retina, skeletal muscle, endothelia, vascular smooth muscle cells, spleen, immunocytes (especially activated macrophages, lymphocytes and dendritic cells) (8–10), sebocytes/sebaceous glands (11) and in keratinocytes (12, 13). PPARγ2 is restricted to adipose tissue. PPARγ is linked to adipocyte differentiation, fatty acid uptake and glucose homeostasis (insulin receptor signalling mechanisms). Its wide expression in the immune system enables PPARγ agonists to have a range of effects on immune and inflammatory responses, including the ability to inhibit activation of monocyte/macrophages, down-regulate dendritic cell function and promote apoptosis of T cells.

STRUCTURE/LIGANDS FOR PPARs

Common to all PPAR proteins, and other nuclear hormone receptors, is their structure consisting of four domains (Fig. 1). These are an amino-terminal region (domain A/B), a DNA binding region (C), a hinge region (D), and the ligand binding, dimerization and trans-activating domain (E/F). Within the A/B domain is the activation function 1 (AF1) region that can operate in the absence of ligand binding. Domain C is structurally conserved across the nuclear receptor superfamily and is folded into two zinc fingers conferring PPARs with their DNA binding specificity. The E/F domain of PPARs comprises 12 α-helical regions denoted H1 to H12. This domain is involved in heterodimerization with RXRs as well as with heat shock proteins (HsPs) and also forms a hydrophobic ligand-binding pocket. In addition, the E/F domain contains an activation function 2 (AF-2) domain which requires the binding of ligand to induce transcriptional activation. The ligand binding pocket of PPARs is much larger than that of other nuclear receptors and PPARs seem to have evolved to bind to multiple, variably sized natural ligands with relatively low affinity. The fact that PPARs bind such a broad range of ligands raises questions about the evolutionary origin of PPARs, but their lipid ligands suggest a role for PPARs in inflammatory processes. PPARα binds natural polyunsaturated fatty acids such as linoleic and arachidonic acids and their derivatives such as eicosanoids products of the lipoxygenase pathway, including 8-S-hydroxytetraenoic acid (8-S-HETE) and leukotriene B4 (LTB4). Synthetic drug ligands for PPARα include the lipid-lowering fibrates. A potent natural ligand for PPARβ/δ has yet to be found. Natural ligands for PPARγ have not yet been identified but a variety of polyunsaturated fatty acids can bind to and activate PPARγ. These include 15-deoxy-Δ12,14-prostaglandin J2 (PGJ2) which is used as an experimental drug. Lipidic acids and 13-Hydroxyoctadecenoic acids and 15-hydroxytetraenoic acid (15-HETE) have also been found to be PPARγ agonists. The thiazolidinedione drugs including troglitazone (now discontinued), rosiglitazone and pioglitazone, used as insulin-sensitizing drugs in the treatment of diabetes, are also ligands for PPARγ. However, it should be noted that the ability of PPARγ to increase sensitivity to insulin in diabetic subjects contraindicates its use in those patients who are insulin-dependent. PPARγ controls the expression of several genes involved in lipid metabolism including lipoprotein lipase, acyl coenzyme A synthase, fatty acid transport protein and phosphoenol pyruvate carboxykinase. These are all involved in coordinating uptake, metabolism and storage of fatty acids.

Drugs that act as isotype-specific ligands have given further insight into various functions of PPARs, as has the generation of PPAR knockout mice. In addition,
newer synthetic, high affinity ligands, such as GW501516 for PPARβ which causes a marked increase in HDL-cholesterol, are being rapidly identified and assessed, further aiding our understanding of the relationship between the receptors and their physiological and pharmacological roles.

ACTIVATION OF PPARs

Most nuclear hormone receptors exist in an inactive form complexed with Hsps and other so-called chaperones including immunophilins. Thus PPARα has been shown to be associated with Hsp72 (17) and also with Hsp90 (18) (Fig. 2). The interaction and formation of complexes with Hsps seems to have an inhibitory effect on the PPAR capacity to interact with DNA and transcription factor activity. PPAR activation and regulation may occur either following interaction with specific ligands or by kinase-mediated phosphorylation, following a variety of extracellular signals. Following binding of ligand, the PPAR undergoes a conformational change and becomes able to interact through the E/F domain with RXR to form heterodimers. These dimers will then interact with the cognate recognition motif (PPREs) in the promoter region of relevant genes to activate transcription of target genes. The PPRE itself consists of two hexameric DNA repeat motifs AGGTCA separated by one or two nucleotides. These grouped sequences, composed of two hexamer half-sites spaced by one or two nucleotides, are termed DR-1 and DR-2, respectively. The organization of these hexameric motifs in repeats or palindromes and the spacing between the hexamers is what determines the specificity of binding of members of the nuclear receptor superfamily including the three PPAR isotypes. It is the pattern of ligand binding and tissue-dependent expression of these isotypes that determines specificity and function.

PPARγ can be activated by phosphorylation of serines within the AFI region of domain A/B. This phosphorylation is performed by mitogen-activated protein kinase (MAPK) in response to environmental changes and extracellular signals such as tissue stress and insulin (16). This increases transcriptional activity independent of ligand binding. Furthermore, C domain phosphorylation by protein kinase A (PKA) has also resulted in increased ligand-dependent PPARγ transcriptional activity. By contrast, PPARγ activity has been shown to be sensitive to phosphorylation by members of the MAPK pathway but in the opposite sense to PPARα (16); thus ERK2 and JNK pathways have been implicated in phosphorylation of specific serines that decreases transcriptional activity. Another consequence of MAP kinase-mediated phosphorylation of PPARγ is to increase the capacity of PPARγ to bind directly other proteins including the Rel A (p65) subunit of NFκB (19) (see below).

BIOLOGICAL EFFECTS OF PPARs

Anti-neoplastic effects

There are numerous analogies between PPARs and retinoids. For example, retinoids have long been known to have anti-neoplastic effects by virtue of their ability to inhibit tumour-promoting mechanisms transduced via transcription factors such as AP-1 (20). Retinoids also induce differentiation in a wide range of normal and malignant cell lines. Similarly, there is evidence that ligands of PPARγ have a variety of anti-neoplastic effects. In vitro, thiazolidinediones are able to inhibit the growth of many types of cancer cell. They can also induce differentiation of normal cells, causing stem cells and precursor cell types to differentiate into adipocytes and myocytes, and can cause malignant cells such as liposarcoma, breast, colon and prostate cancer cells to undergo differentiation. In addition, PPARγ ligands can induce apoptosis of many different tumour cell lines (21). Furthermore, PPARγ agonists can inhibit both tumour growth and metastasis in animal models (22, 23). One important anti-tumour mechanism is inhibition of angiogenesis (see below). However, the promise from in vitro and murine studies has not yet been realized in treatment of human cancers. Thus, oral administration of troglitazone to 25 patients with chemotherapy-resistant metastatic colon cancer had no effect on
The above findings are somewhat difficult to interpret in light of the results in adult PPARβ/δ heterozygous mutants which exhibited increased keratinocyte proliferation with a marked exaggeration in the hyperplastic response to tetradecanoyl phorbol acetate (TPA) (31). In mice, after birth, PPAR expression in interfollicular epidermis decreases to undetectable levels. However, all three isotypes are still seen within hair follicles. On proliferative stimuli such as hair plucking, application of TPA or wounding, PPARα and PPARβ/δ are seen once more in interfollicular skin. Generation within the epidermis of 8S-hydroxyicosatetraenoic acid (8S-HETE), an endogenous ligand for PPARα, by overexpression of 8S-lipoxygenase (the enzyme which generates 8S-HETE), resulted in increased differentiation of the keratinocytes as reflected by keratin-1 synthesis (32). PPARα agonists (clofibrate, oleic or linoleic acids) also accelerate rat epidermal maturation in an in vitro explant system; ligands for PPARβ/δ or PPARγ were without effect (33).

Adult human keratinocytes express the three PPAR isoforms, PPARβ/δ being most prominent (3, 4). Ex vivo human keratinocyte differentiation is associated with an increase in the proportions of PPARα and PPARγ expressed, whereas PPARβ/δ expression remains stable. However, in hyperproliferative states such as psoriasis, PPARα and PPARγ diminish as PPARβ/δ increases in the epidermis. PPARα agonists increase the expression of differentiation markers involucrin and transglutaminase and enhance the synthesis of epidermal lipids important in the stratum corneum permeability barrier (28, 34).

PPARs and wound healing

Following skin injury, wound healing proceeds via an overlapping pattern of events including inflammation, re-epithelialization, and matrix and tissue remodelling. The sequence of these events is regulated, temporally and spatially, by a variety of growth factors and cytokines that co-ordinate the balance between inflammation and tissue regeneration. One of the major processes contributing to the closure of a wound is the process of re-epithelialization, which is a combination of migration and enhanced proliferation of keratinocytes in the wound edge. In adult murine skin, PPARs are not expressed in interfollicular epidermis; however, following wounding, the expression of PPARβ is rapidly stimulated to high levels in the wound edges. This augmented expression lasts throughout the wound closure process. PPARα is also induced but to a lesser degree and the expression is short-lived, reducing after about 3 days when the main inflammatory phase subsides (6). The major stimulant for PPARβ up-regulation is tumour necrosis factor (TNF)-α generated as part of the inflammatory response to tissue injury (35). Not only is the expression of the PPARβ receptor augmented, but there is also generation of ligands able
to activate the receptor (35). The role of PPARβ in wound healing has been elucidated from in vitro observations in wild-type and PPARβ knockout keratinocytes and in vivo observations in PPARβ<sup>−/−</sup> heterozygous mice (reviewed by Tan and colleagues 36). Overall, PPARβ null keratinocytes exhibit impaired attachment and migration and increased susceptibility to apoptosis in vitro (36). In vivo, the PPARβ<sup>−/−</sup> heterozygous mice show delayed wound re-epithelialization mainly because despite increased keratinocyte proliferation there is also increased keratinocyte apoptosis.

The role of PPARs in the wound healing processes in humans has yet to be investigated in detail. PPARβ/δ is the most abundantly expressed receptor in human epidermis (3, 4) and only a PPARβ-selective ligand, but not PPARα or PPARγ ligands, induced the expression of keratinocyte differentiation markers (3). No doubt the role of these receptors in wound healing and injury repair in humans will be explored in the foreseeable future.

**Anti-inflammatory effects of PPARs**

**PPARα.** The involvement of PPARs in inflammatory processes is suggested from the observation that PPARα-deficient mice display increased inflammatory responses with prolonged inflammation to LTB<sub>4</sub> and increased production by splenocytes of cytokines interleukin (IL)-6 and IL-12 in response to lipopolysaccharide (LPS) (37). Activation of PPARα with agonists has inhibitory effects on several inflammatory responses in vivo and in vitro. Thus, in mice, topical application of the PPARα agonists clofibrate, WY-14,643 or linoleic acid inhibited the inflammatory response induced by TPA in terms of both oedema and cellular infiltrate (38). Although the authors called this an ‘irritant’ response, TPA has very different effects in murine skin compared with human skin; indeed, as TPA is a potent tumour promoter, it may be that the equivalent response in humans would be that induced by UVB (see below). Topical PPARα agonists also inhibited the specific immunological responses of allergic contact hypersensitivity to oxazolone – but significantly less than that seen with the potent topical glucocorticoid clobetasol propionate (38). In human volunteers, topical application of WY-14,643 significantly inhibited erythema induced by UVB (39). In addition, PPARα agonists clofibrate and WY-14,643 reversed UVB-induced mRNA and protein expression of IL-6 and IL-8 by keratinocytes (HaCaT cells) (39).

PPARα agonists inhibit production of IL-2 and TNF-α as well as release of interferon (IFN)-γ by activated T lymphocytes (40). PPARα also reduces cytokine-mediated expression of adhesion molecules such as vascular cell-adhesion molecule-1 (VCAM-1) (41, 42), TNF-α-induced expression of intercellular adhesion molecule-1 (ICAM-1) (42) and thrombin-induced endothelin-1 expression in endothelial cells (43).

The mechanisms by which PPARα inhibits this range of inflammatory processes are probably mediated through inhibitory interactions with the key transcription factors NFκB and AP-1. These transcription factors are each ‘master switches’ that activate expression of a whole group of molecules with key roles in inflammatory processes. PPARα inhibits activation of NFκB via two mechanisms: first, PPARα interacts directly with the Rel homology domain of the p65 subunit of NFκB (16, 44, 45). The second mechanism by which PPARα represses activation of NFκB is by induction of expression of IκBα, the major inhibitor of NFκB (44). PPARα can also inhibit the AP-1 signal transduction pathway by interaction with c-Jun (46). Moreover, there is a reciprocal interaction between the pathways in that activation of AP-1 also inhibits expression of PPARα (46).

**PPARγ.** Overall, PPARγ can interfere with many components of the inflammatory response by altering expression of cytokines, receptors and adhesion molecules by T cells, monocyte/macrophages, vascular smooth muscle cells and endothelial cells (16). Activation of T lymphocytes via the T-cell receptor (CD3) induces secretion of IFN-γ, a response which is inhibited in a dose-dependent fashion by PPARγ ligands pioglitazone and rosiglitazone (40). PPARγ is markedly up-regulated in activated macrophages and inhibits the expression of inducible nitric oxide synthase (iNOS) and gelatinase B (47), but conversely PPARγ agonists induce release of NO from endothelial cells (48) and up-regulate NOS in vascular smooth muscle cells (49). Production by macrophages of pro-inflammatory cytokines TNF-α, IL-1β, IL-6, RANTES and MCP-1 is suppressed by PPARγ agonists (50, 51). However, according to Chawla et al., the concentrations of PPARγ agonists required for these inhibitory effects on macrophages are much higher than their respective dissociation constants (52), and there is evidence that the inhibition of macrophage expression of a range of cytokines is in fact independent of the PPAR-γ receptor (52). Thus, 15-deoxy-Δ<sub>12,14</sub> prostaglandin J<sub>2</sub> (PGJ<sub>2</sub>) the natural ligand for PPARγ, potently inhibited expression of TNF-α and IL-6 in macrophages but this activity was not diminished when the macrophages lacked PPARγ receptors. This interesting observation suggests that some ligands for PPARγ may have direct actions on signal transduction components or may have actions on other PPARs or even other receptor systems.

Like PPARα, PPARγ can interact with a range of key transcription factors including NFκB, AP-1, NFAT and STAT-1 (53), and this interaction can result in inhibition of these important mediators. PPARγ inhibits effects mediated via NFκB by three possible mechanisms (Fig. 3). First, activation of PPARγ by ligands causes
endothelial cells, proliferation and formation of patent tubular vessels. Vascular endothelial cell growth factor (VEGF) is a potent endothelial cell-specific mitogen. It is secreted as a homodimer of 40–45 kDa with four isoforms (from alternative splicing) and binds to two high affinity receptor tyrosine kinases, KDR and Flt-1. It stimulates growth of new capillaries from pre-existing blood vessels, and causes vascular hyperpermeability.

PPARγ agonists have diverse effects on the expression of VEGF and its downstream effects. Thus, in vascular smooth muscle cells and in macrophages, PPARγ ligands increase the generation of vascular endothelial growth factor (51, 55) – which might be expected to have pro-angiogenic effects. However, PPARγ ligands are potent inhibitors of angiogenesis in vitro and in vivo (56). Human umbilical vein endothelial cells grown in collagen gels are able to form tube-like structures in response to pro-angiogenic stimuli including VEGF and basic fibroblast growth factor in combination, and agonists of PPARγ (but not PPARδ) inhibited this tube formation in a dose-dependent manner (56). In addition, corneal neovascularization induced in vivo by implantation of VEGF-impregnated sponges is significantly inhibited by PPARγ ligands (56). It appears that the anti-angiogenic mechanism in this model is via inhibition of transcription of mRNA encoding the major receptors KDR and Flt-1 through which VEGF acts.

**PPAR AGONISTS AND PSORIASIS**

Psoriasis is characterized by hyperproliferation and altered differentiation of the epidermis, an inflammatory reaction in the dermis and microvascular proliferation with formation of abnormal dilated and tortuous capillaries. Although the primary cause(s) and pathogenesis of psoriasis are not understood, there are clues to be found from the analysis of the mechanisms of therapeutic agents effective against this condition. Interestingly, several agonists of the nuclear hormone receptor family have anti-psoriatic effects. These include glucocorticoids, retinoids and vitamin D derivatives. Hence, it should not come as a surprise that PPAR agonists are also anti-psoriatic. It was first observed that the thiazolidinedione agent troglitazone could ameliorate psoriasis (57). The same group went on to show that PPARγ receptors were expressed by cultured keratinocytes and that administration of PPAR agonists, including troglitazone, inhibited keratinocyte proliferation in vitro (58). More recently, it has also been shown that the newer thiazolidinediones, rosiglitazone and pioglitazone, also inhibit keratinocyte proliferation (12), with pioglitazone being more potent than troglitazone. Rosiglitazone also inhibited keratinocyte motility and production of matrix metalloproteinases -1 and -9 by human skin organ cultures (12). We have shown in a small pilot study that pioglitazone has clinically
significant anti-psoriatic effects (59). Interestingly, topical use of a range of PPAR agonists was found to be ineffectual against psoriasis (60). This raises the question as to whether sufficient percutaneous absorption occurred to produce therapeutically effective drug concentrations or whether the fundamental mechanisms affected by PPAR agonists are in fact systemic. The full clinical efficacy of PPARγ agonists in the treatment of psoriasis needs to be established in properly controlled double-blind trials. It will then become most interesting to determine which cellular components are most affected by the PPARγ agonists.

A recent case-control study has examined the possibility that there may be an association between psoriasis and the genes encoding PPARα or PPARγ (61). They looked at the frequencies of single nucleotide polymorphisms (SNPs) in these two genes but found no differences between patients with psoriasis and healthy controls. This suggests that the investigated SNPs within these two PPAR genes do not promote susceptibility to psoriasis, but based on the fact that a limited number of SNPs were examined, it is possible that other genetic alterations in these genes could play a role in psoriasis development. In addition, because there is evidence that certain SNPs in the PPARG gene may affect the function of the receptor, further research will be necessary to address whether these SNPs alter responses of patients with psoriasis to thiazolidinediones.

CONCLUSIONS
The PPARs affect a wide range of biological processes, many of which are important in the skin. Their effects on keratinocyte growth and differentiation and their modulation of inflammation, angiogenesis and wound healing make it unsurprising that they have anti-psoriatic effects. As the range of activating ligands with greater specificity for each PPAR isoform is extended, so the functional role of the different PPARs will become clearer. Also, therapeutic experiments using combinations of ligands that activate different members of the nuclear receptor superfamily have the potential to produce yet more effective therapies, not only for psoriasis but conceivably, for keratinocyte dysplasia. The obvious candidate is ultraviolet-induced carcinogenesis which involves the combination of inflammatory and growth-modifying effects that the nuclear receptor family seem able to antagonize. This group of receptors and the drug agents that act through them are only just penetrating into the field of dermatology, but the signs indicate that in the near future they will come to occupy an important place.

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