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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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The nuclear hormone receptors are a family of intracellular receptors that allow cells to respond to extracellular signals through the binding of their relevant ligands; the family includes the receptors for steroid hormones, thyroid hormones, vitamin D and retinoids. Peroxisome proliferator-activated receptors (PPARs) are members of this nuclear receptor superfamily and, similar to the other members of the family, function primarily as ligand-dependent transcription factors whereby, upon ligand binding, they activate genes which contain PPAR-responsive elements (PPREs) in their promoter. Their name derives from their ability to interact with various fatty acids, their derivatives and certain hypolipaemic xenobiotics to cause peroxisome proliferation in the liver. Since the discovery of PPARα in 1990 by Isseman & Green (1), two further isoforms, PPARβ (also known as PPARδ) and PPARγ, have been described. Each isotype is encoded by a different gene, and has distinct tissue distribution and actions as a result of their differing ligand-binding domains. The nuclear receptor superfamily has a crucial role in almost every aspect of mammalian cell development and physiology, and there is evidence that PPARs similarly play a significant role in many areas of biology and in particular in skin homeostasis. On binding of ligand, PPARs undergo a conformational change enabling them to form a heterodimer with the 9-cis retinoic acid receptor (RXR). The PPAR/RXR complex forms a transcription factor able to bind to DNA at PPREs, which are DNA sequences specifically capable of 'recognition' and binding by the DNA-binding component of this transcription factor. A large number of PPAR target genes have been identified with wide-ranging effects on cell proliferation, differentiation, inflammatory responses and angiogenesis, as well as lipid and glucose metabolism.

PEROXISOMES

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_2O_2 through a group of oxidizing enzymes which use molecular oxygen to transform their substrates, releasing H_2O_2 and OH which can be toxic. The oxidative stress resulting from H_2O_2 is known to stimulate phospholipase D, which is associated with the production of phosphatidic acid and diacylglycerol. These in turn affect adenylyl 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.

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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 (2), vascular smooth muscle and at low levels in keratinocytes (3, 4). 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 (5) but despite being the most ubiquitously expressed is perhaps the least understood. It is the dominant subtype expressed by keratinocytes in human skin (3, 4). 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 hyperproliferation, induces expression of PPARα and PPARδ – PPARα seems to be important in the inflammatory phase while PPARδ is important for cell migration and re-epithelialization (6, 7).

PPARγ exists in two main isoforms 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 (14) and promote apoptosis of T cells (15).

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 (16). 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 eicosanoid products of the lipoxygenase pathway including 8-S-hydroxytetraenoic acid (8-S-HETE) and leukotriene B_4 (LTB_4). 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-$\Delta^{12,14}$ prostaglandin J_2 (PGJ2) which is used as an experimental ligand. 9- and 13-Hydroxyoctadienoic acids and 15-hydroxytetraenoic acid (15-HETE) have also been found to be PPARγ activators. 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,

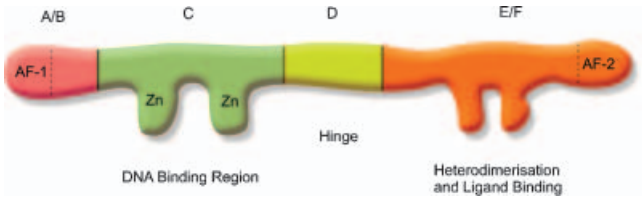

Fig. 1. Structural organization of PPARs. A/B=transactivation and phosphorylation domain; C=DNA-binding domain with two zinc fingers which binds to PPAR response elements in promoter regions of responsive genes; D=hinge region; E/F=ligand-binding and heterodimerization with heat shock proteins and/or RXR. AF-1=ligand-independent activator function – this can be activated by phosphorylation via MAP-kinases; AF-2=ligand-dependent activator function.

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.

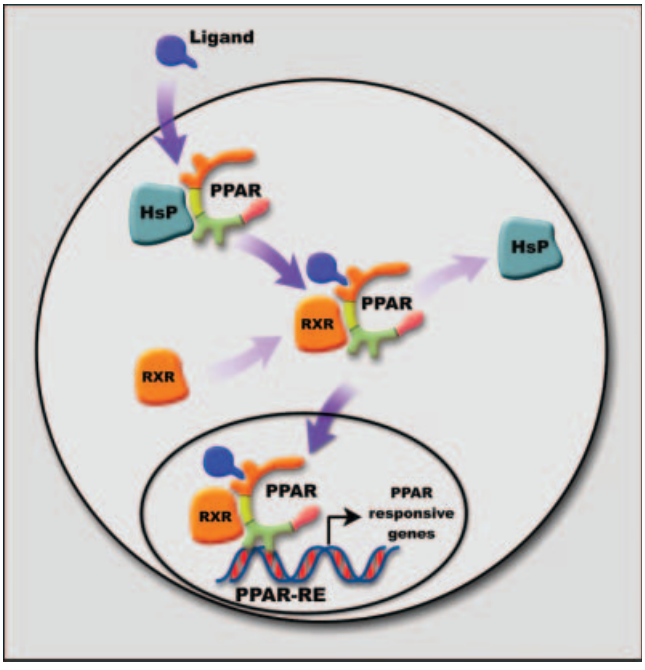

Fig. 2. PPARs are held in inactive complex associated with heat shock proteins (HsP). Following binding with ligand or other activation signals (see Fig. 3), HsP is replaced with retinoic acid receptor (RXR) forming active transcription factor. The active PPAR/RXR heterodimer binds to PPAR response element AGGTCA X AGGTCA to initiate transcription of relevant genes.

PPARα can be activated by phosphorylation of serines within the AF1 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 PPARα 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 EFECTS 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

disease progression or median survival time (24). Similarly, the use of troglitazone to treat 22 patients with advanced refractory breast cancer resulted in no beneficial effects (25), although this study was not completed because it coincided with the withdrawal of troglitazone from the market. Unfortunately, the big problem that besets this field is that by starting with the very worst cases of therapy-resistant cancers, the clinical trials have set an almost impossible task for these drugs. It is to be hoped that when the newer thiazolidinediones are used in much earlier stage disease or in situations with a high likelihood of progression to malignancy such as adenomatous polyposis coli or xeroderma pigmentosum, they may have a much better effect at preventing the progression of early, premalignant lesions to the full blown malignancy.

Epidermal structure, function and differentiation

In addition to the well documented effects of PPARs on gene transcription associated with lipid metabolism and energy homeostasis, more recently roles in epidermal maturation, repair and angiogenesis have been highlighted. The fact that altered proportions of expression of the three isotypes mirrors the sequential expression of markers of differentiation, such as keratins, involucrin and loricrin, as well as the processing and organization of the stratum corneum hydrophobic barrier, led to the hypothesis for a specific role for PPARs in regulating these complex processes and a role in disease pathogenesis.

Skin development is regulated by a number of nuclear hormone receptors and their ligands. Thyroid hormones, testosterone, oestrogens and glucocorticoids all hasten epidermal barrier maturation (26). Although PPAR expression parallels epidermal differentiation in both humans and mice, it remains to be demonstrated whether events are under their direct regulation.

Interestingly, PPARs seem to show species-dependent differences in their regulatory activities. This makes extrapolation from their role in animal models of skin disease to humans more perilous. Activation of PPARα with fatty acids or other ligands accelerates fetal skin development, induces differentiation in keratinocytes, inhibits keratinocyte proliferation and improves permeability barrier function (27–29). PPARα null and PPARβ/δ heterozygous mutant mouse models show normal skin architecture in the embryonic stage and differentiation markers seem unaffected, with normal skin histology in the adult PPARα null mice. However, activation of PPARβ/δ with a specific ligand GW1514, while having little effect on keratinocyte proliferation, augments differentiation (as reflected by loricrin expression) (30). Also, in mice treated topically with GW1514, following damage by tape stripping, the epidermal permeability barrier was reconstituted more rapidly (30). 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-hydroxyeicosatetraenoic 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 upregulation 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$^{+/-}$ 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$^{+/-}$ 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_4 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-$\Delta^{12,14}$ prostaglandin J_2 (PG J2) 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

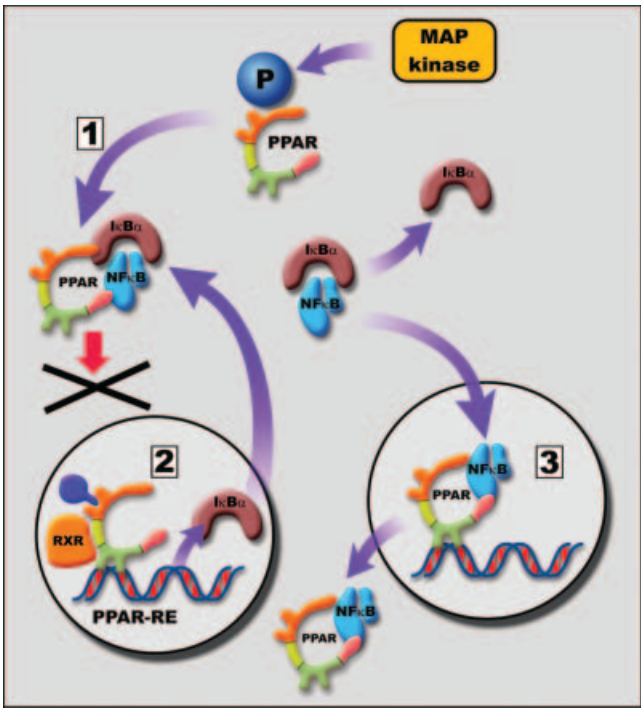

Fig. 3. Interaction of PPARγ with NFκB via three different mechanisms. (1) Following external activation signals, MAP kinases phosphorylate PPARγ which can then interact directly with IκBα preventing it from dissociating from the NFκB complex, hence preventing activation of NFκB. (2) PPARγ becomes activated, heterodimerizes with RXR, binds to the PPRE in the promoter of IκBα. IκBα is synthesized and inactivates any free/active NFκB heterodimers. (3) Activated PPARγ binds with the Rel A (p65) chain of NFκB heterodimer, preventing it binding to the NFκB-RE and facilitating its export from the nucleus.

it to heterodimerize with RXR, thus forming a ligand-dependent transcription factor able to up-regulate transcription of IκBα, the main inhibitor of NFκB (44). Second, the ligand for PPARγ can directly activate MAPK independently of PPARγ. This results in phosphorylation of the PPARγ which can then bind to the NFκB/IκB complex, inhibiting phosphorylation and dissociation of IκB (19). Thirdly, conditions induced in gut epithelial cells by non-pathogenic *Bacteroides* species result in binding within the nucleus of PPARγ to the Rel A (p65) chain of NFκB. This newly formed complex is rapidly exported from the nucleus, resulting in reduction of the NFκB transcriptional effects on many pro-inflammatory cytokines. PPAR-γ activation also has effects on the transcription factor NFAT, through which it inhibits IL-2 production by T lymphocytes (54); the activated PPARγ physically associates with NFAT, blocking NFAT DNA binding and transcriptional activity regulating the IL-2 promoter.

Effects on angiogenesis

Angiogenesis involves degradation of basement membranes by proteases, penetration and migration of 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 PPARα) inhibited this tube formation in a dose-dependent fashion (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 rosiglitazone being more potent than pioglitazone. 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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