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Peroxisome proliferator-activated receptors (PPARs) in dermatology

Challenge and promise

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Since their discovery it has become clear that peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors involved in the genetic regulation of the lipid metabolism and energy homoeostasis. Subsequently, accumulating evidence suggests a role of PPARs in genomic pathways including the regulation of cell growth, apoptosis and differentiation. These findings indicate that PPARs and PPAR agonists play an important role in inflammatory responses and tumor promotion. Because of their diverse biologic activities on keratinocytes and other skin cells, PPARs represent a major research target for the understanding and treatment of many skin pathologies, such as hyperproliferative and inflammatory diseases. Overmore recent clinical trials identified PPARs as promising drug targets for the prevention and treatment of various diseases in the field of dermatology. The present review summarizes the current knowledge of PPAR functions in various skin disorders particularly those involving inflammation and epidermal hyperproliferation (i.e., psoriasis, atopic dermatitis, acne, scleroderma, skin malignancies).

Introduction

The PPARs belong to a subfamily of nuclear hormone receptors compromising three different isoforms of PPARs termed PPARα, PPARβ/δ and PPARγ.[1] These subtypes are encoded by separated genes, exhibit different tissue distribution and functions and, to some extent, different ligand specificities.[2] After ligand binding, PPARs can regulate gene expression by binding to peroxisome proliferator response elements (PPRE) in target genes as heterodimers with the retinoid X receptors (RXR).[3] Activation of the PPARs have been shown to play an important role in the regulation of energy homeostasis by modulating glucose and lipid metabolism and transport.[4] Moreover recent studies have demonstrated that PPARs regulate important cellular functions in the skin and other organs, including inflammation, immune responses, cell proliferation, cell differentiation and apoptosis. Knowing that several of the most common skin diseases (i.e., psoriasis and atopic dermatitis) are characterized by a spectrum of abnormalities, including abnormal keratinocyte differentiation, epidermal hyperplasia, inflammation and defects in permeabilitiy barrier function, PPARs and their corresponding ligands are potential targets in treating various skin diseases.[5,6]

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Inflammation and Wound Healing

During embryonic development, the epidermis evolves from a single layer of epithelial cells to a fully stratified and differentiated epithelium. After birth, progenitor undifferentiated keratinocytes undergoing a vectorial differentiation continuously migrate from the basal to the uppermost layer. Keratinocyte differentiation is a complex, sequential process including the sequential expression of structural proteins (keratins, involucrin, loricrin and filaggrin), the processing and reorganization of lipids (sphingolipids, free fatty acids and cholesterol) and finally, cell death.[7] This important process leads after an injury to the covering of the wounded area with a newly differentiated protective epidermis. Wound healing has traditionally been divided into three distinct phases: the initial inflammatory stage of repair is followed by the proliferation and migration of keratinocytes, and a process called remodeling.[8,9]

Ultraviolet B (UVB) irradiation led to a decrease of all three peroxisome proliferator-activated receptor subsets at the mRNA level, which may be consistent to a exaggerated and prolonged inflammation. Kippenberger et al. showed that topically applied PPARα agonists increased the minimal erythema dose in UVB-irradiated skin.[10] Topical or systemic application of PPARα activators or compounds that positively regulate PPARα gene expression may therefore help to counteract exaggerated inflammatory processes. Further investigations have to show in how far a prophylactic treatment with PPAR activators before sunbathing may help to reduce the adverse effects of UVB.

After injury the expression of PPARα and PPARβ/δ, but not of PPARγ, is upregulated in keratinocytes at the wound edge of damaged skin. While the expression of PPARα is transiently upregulated during the early inflammatory phase of healing, that of PPARβ/δ remains expressed until completion of the healing process.[11] The expression of PPARβ/δ is increased via binding of the activator protein-1 (AP-1) transcription factor complex to its promotor, triggered by the activation of the stress associated protein kinase pathway by pro-inflammatory cytokines, such as

tumor necrosis factor-α (TNFα) and interferon-γ.[12] The release of pro-inflammatory cytokines triggers the production of PPARβ/δ ligands, leading to an increase in keratinocyte PPARβ/δ transcriptional activity in wounded epithelium. Once epithelization is completed, TNFα-induced PPARβ/δ expression is repressed by transforming growth factor-β1 (TGFβ1) signaling, which inhibits AP-1 binding to the PPARβ/δ promoter.[13] In summary, PPARα and PPARβ/δ appear to be key mediators of epidermal effects in wound healing by converting the extracellular inflammatory signal into an organized pattern of gene expression, leading to survival, migration and differentiation of keratinocytes.[14]

Psoriasis

Knowing that psoriasis is an inflammatory skin disorder characterized by epidermal hyperproliferation and abnormal differentiation of keratinocytes, PPARs may be interesting targets for treatment. In psoriatic skin expression of both PPARα and PPARγ is decreased, whereas PPARβ/δ expression is increased.[15,16] This increase of the PPARβ/δ expression is probably due to pro-inflammatory signals, a condition reminiscent of that following skin injury. Interleukin (IL)1- and STAT3-related signaling was identified to be regulated by this activation of PPARβ/δ in the epidermis.[17] In addition to the increased PPARβ/δ expression levels, numerous lipid molecules, such as lipoxygenase products, which are potent activators of PPARs in human keratinocytes, accumulate in the psoriactic lesions.[18] Overmore the activation of PPARβ/δ in the epidermis was shown to be sufficient to trigger inflammatory changes, immune activation and gene dysregulation characteristic of psoriasis.[17] Studies in a mouse model of hyperproliferative skin disease have shown that topical administration of PPARγ ligands reduced epidermal hyperplasia and that the treatment had no effect on normal skin.[19] Pilot studies with psoriatic patients showed that PPARα (clofibrate), PPARβ (tetradecylthioacetic acid) and PPARγ (rosiglitazone) agonists did not normalize skin homeostasis when topically applied on plaque psoriasis.[20] Interestingly in patients suffering from chronic, stable plaque psoriasis orally administrated thiazolidinediones (TZDs), a group of synthetic PPARγ ligands licensed as insulin-sensitizing drugs, showed a therapeutic benefit.[16,21,22] These observations indicate that systemic, but not local activation of PPARγ is beneficial. The exact mechanism of this is still unknown since Mao et al. showed that PPARγ-activated keratinocyte differentiation and decreased cutaneous inflammation by TZDs is not dependent on PPARγ in keratinocytes.[23] Although all PPAR isotypes act to various degrees on the pathogenic factors for psoriasis, it is not presently possible to distinguish an isotype that would be most useful in the treatment of psoriasis. In summary PPARβ/δ seems to be of particular importance, as judged by in vitro and in vivo studies, while PPARγ seems to be important clinically, as oral administration has been reported to improve psoriasis.

Atopic Dermatitis

It was long thought that atopic dermatitis (AD) is solely attributable to immunological defects. Evidence is accumulating that primary keratinocyte abnormalities may underlie the pathogenesis of this skin disorder in many patients. Among others PPARs reduce certain inflammatory mediators in the skin and regulate epidermal barrier homeostasis, alterations of which contribute to the inflammation associated with AD. It has been shown that PPAR ligands inhibit T helper cell (T_H) responses in terms of inhibition of IL-2 production by T cell clones, while not inhibiting proliferation of such clones.[24] Especially PPARγ play a critical role in the regulation of genes that are involved in cellular proliferation, specific components of the T_H2 inflammatory pathway and maintenance of the skin barrier.[20] This suggestion was supported by the observation that the PPARγ ligand ciglitazone inhibits allergic immune response by inhibiting T_H2-driven IgE production and also production of (pro)inflammatory cytokines of the T_H response in vitro and in vivo.[25] Recent analysis of AD skin lesions show increased PPARγ expression not only in keratinocytes, but also in infiltrating T cells and monocytes.[26] The same group demonstrated that systemic applicated ciglitazone inhibits not only systemic but also local inflammatory immune response in the skin by diminishing the severity of allergen-induced dermatitis.[27] Systemic treatment with the PPARγ agonist rosiglitazone, an other member of the TZDs, let to a decreased total body surface area involvement, severity of lesions and number of flares in patients with severe AD.[28] Beside this topical treatment with a PPARα agonist had a beneficial effect for childhood atopic dermatitis allowing to spare dermocorticoids and improving the quality of life.[29]

Acne

The pathophysiology of acne centers on the interplay of follicular hyperkeratinization, inflammation induced by Propionibacterium acnes and the production of sebum that serves as a nutrient source for bacteria.[30-32] Because of the many similarities that exist between adipogenesis and sebaceous lipogenesis PPARs may be important in the regulation of human sebum production and the development of acne.[33-35] Studies in sebocytes and human sebaceous glands indicate that PPAR agonists alter sebaceous lipid production.[36] In addition to this, PPAR regulation can modulate the tissue inflammation in acne lesions by inhibiting the expression of proinflammatory genes.[37,38] Recent evidence indicates a role for lipoxygenase products, such as leukotrienes B_4 (LTB_4), in the development of inflammatory acne lesions.[39,40] Interestingly, LTB_4 is also a natural ligand for peroxisome proliferator-activated receptor PPARα.[38,41] Recently Zouboulis reported that systemic treatment with the lipoxygenase inhibitor Zileuton reduces the inflammatory lesions in acne patients with the concomitant decrease of sebum hydroperoxides amount, indicating that these compounds have a role in the pathogenesis of acne exerting proinflammatory activity on the pilosebaceous unit.[42] Zileuton inhibited sebum synthesis to a similar level with that of low-dose isotretinoin.[43] The exact mechanism is still unknown. However in agreement with the ability of Zileuton to inhibit LTB_4 formation, an effect on PPARs can be implicated.[42]

Scleroderma

The hallmark of systemic sclerosis is the excessive collagen accumulation in the skin and the lungs leading to organ dysfunction, failure and death.[44] The pathogenesis of fibrosis remains incompletely understood.[45] Recently the paradigm that inflammation leads to fibrosis has been supplanted by the concept that inflammation and fibrosis may be independent of each other.[46,47] Therefore the focus on developing new treatments for fibrosis has shifted to target both the anti-inflammatory and fibrogenic process. It has been recognized that PPARγ agonists have antifibrotic properties too, characterized by inhibition of pulmonary myofibroblast differentiation and collagen production als through mechanisms other than direct targeting of PPARγ.[48,49] This effects were in part induced by transforming growth factor (TGF)β, leading to an activation of fibroblasts with increased collagen production, expression of cell surface receptors for growth factors, secretion of cytokines and chemokines, resistance to apoptosis induction and myofibroblast differentiation.[50] Deletion of PPARγ resulted in enhanced susceptibility to bleomycin-induced skin fibrosis, as indicated by increases in all measures of skin fibrosis and enhanced sensitivity of fibroblasts to TGFβ in PPARγ-deficient mice.[51] In a murine model of subcutaneous bleomycin-induced scleroderma systemic administration of the PPARγ agonist rosiglitazone inhibited early inflammation responses and abrogated skin fibrosis, local collagen accumulation, lipoatrophy and reduced tissue accumulation of myofibroblasts.[52] In vitro rosiglitazone reduced PPARγ expression and alleviated the persistent fibrotic phenotype of skin scleroderma fibroblasts and may be therefore considered as a possible new treatment for scleroderma.[53]

Non-Melanoma Skin Cancer (NMSC)

As discussed above, studies have shown that PPAR activation can regulate proliferation and differentiation of different cell types and therefore induce growth arrest and apoptosis in a variety of cancer types.[54-56] Selective ablation of RXRα and PPARγ in keratinocytes of mice was shown to enhance DMBA/TPA-induced epidermal tumorigenesis.[57] RXRα/PPARγ heterodimers most probably mediate epidermal tumor suppression. Beside this PPAR ligands have anti-inflammatory properties and inhibit angiogenesis.[58] The contribution of arachidonic acid metabolites to PPAR activation, in particular, LTB_4 for PPARα and prostaglandin J2 for PPARγ, suggest the relevance of PPARs in the regulation of inflammation.[41,59] Moreover, PPAR activators may directly downregulate or inhibit cyclooxygenase-2 (COX-2) expression which is increased in cutaneous squamous cell carcinoma (SCC).[60-62] The therapeutic potential of the link between COX-2 and the PPARs may be used to inhibit UV-induced skin tumor progression.[63] Moreover, the combination of PPAR agonists and COX inhibitors may have synergistic effects.[64] In the skin, PPAR anti-inflammatory response which may affect antitumor immune response has been confirmed by observations that showed that the use of these activators increased the minimal erythema dose.[65] In a mouse model topical application of PPARα agonists reduced the adverse effects of UVB.[66] These observations suggest that PPARα ligands may have chemoprophylactic properties in the prevention of early stages of cancer or its precursor lesions such as actinic keratosis (AK).[64,67]

Other experimental studies showed that PPAR ligands are potent inhibitors of tumor-induced angiogenesis, a process that leads to the formation of new blood vessels, which is a prerequisite for tumor growth, invasion and metastasis of cancer.[68-70] In a clinical trial, the incidence of AK and, to a lesser extent, NMSC decreased significantly in high-risk patients who were on a low-fat diet compared to those on normal diets.[71] Because fatty acids are common activators of PPARs, these proteins may provide the missing molecular link between high-fat diets and nutritionally sensitive cancers. More studies are warranted to investigate the mechanisms by which PPARs affect skin carcinogenesis and how oraly administrated PPAR agonists (in the form of natural fatty acids or synthetic drugs) can influence NMSC development.

Melanoma

Over the past three decades the incidence of malignant melanoma has significantly rised worldwide as a consequence of excessive exposure to sunlight.[72,73] Despite advancements in early diagnosis and treatment, metastasized malignant melanoma has a very poor prognosis.[74] One reason could be that molecular mechanisms involved in skin repair, skin carcinogenesis and melanoma growth are still poorly understood. So far there are only little available therapies for metastatic melanoma. In addition to active prevention and early detection of melanomas, it appears necessary to develop new therapeutic substances to improve the outcome of patients with metastatic melanoma.

In addition to NMSC, evidence is accumulating that PPAR ligands also had mild antiproliferative effects in melanocytes and human melanoma cells.[75-78] Whether this inhibition of cell proliferation is induced by apoptosis or through specific PPAR-dependent pathways is not clear. Correlating to the antiproliferative effects, the vitamin D receptor (VDR) expression was increased in the melanoma cell line MeWo by some PPAR ligands at the same time-point.[78] This gave an indication of an interconnection of the PPAR and VDR signaling pathways at the level of cross-regulation of their respective transcription factor mRNA levels. The complete mechanisms and the physiological and pathophysiological relevance of this cross-talk are not yet known, but may open new perspectives for treatment and/or prevention of melanoma.

In addition to the observed antiproliferative effects, PPARα activation by fenofibrate, a lipid-lowering drug, caused inhibition of migration and anchorage-independent growth both in B16F10 mouse melanoma cells and in human SkMel188 cells in vitro.[79] In Bomirski hamsters with melanoma subcutaneous tumors oral administration of fenofibrate led to significantly fewer metastatic foci in the lungs.[80] However, primary tumor growth remained unaltered. In clinical trials significantly fewer melanoma were diagnosed in patients treated with lipid-lowering drugs (i.e., gemfibrozil) compared with the control group.[81] Nevertheless a recently published metaanalysis could not confirm this observation.[82]

Studies with thiazolidinediones (PPARγ ligands) demonstrated inhibition of colony forming by arresting melanoma cells in the G_1 phase, leading to inhibition of tumorigenesis in nude mice.[83] Especially for ciglitazone the antiproliferative effects were mediated by cell cycle arrest through a PPARγ-dependent pathway at low concentrations. At higher concentrations a major part of the antitumoral activity is mediated through the induction of apoptosis independently of PPARγ.[58,77]

In addition to the synthetic PPAR ligands it has been shown that naturally PPAR agonists like fatty acids inhibit melanoma cells. Especially dietary ω-3 polyunsaturated fatty acids (PUFA) like for example eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have shown to decrease the COX-2 mRNA expression and in consequence invasion in brain-metastatic melanoma, whereas ω-6 PUFA such as arachidonic acid promote the growth of tumor cells.[84] Cario-André suggested that an ω-6 PUFA rich-diet may increase oxidative damage in melanocytes without inducing apoptosis, the long-term net outcome could be cumulated mutations and an increased risk of skin cancer, especially melanoma, whereas ω-3 PUFA are rather protective.[85] Although the relationship between dietary ω-3 PUFA and carcinogenic risk factors is inconclusive, the evidence suggests that increasing dietary ω-3 PUFA is beneficial.[84]

First clinical studies using PPAR ligands as a supplementary agent in melanoma treatment show promising results. A combined treatment with PPAR agonists and COX-2 inhibitors seems to have not only synergistic effects in NMSC prevention, but may also increase the susceptibility of malignant cells to pulsatile chemotherapy by upregulating proapoptotic cellular mechanisms.[86] Administration of pioglitazone (PPAR ligand) and rofecoxib (COX-2 inhibitor) combined with low-dose metronomic trofosfamide prolonged the progression-free survival of patients with treatment-resistant metastatic melanoma compared to treatment with trofosfamide alone.[87] The same group showed that patients with PPARγ-positive metastases and biomodulatory metronomic chemotherapy alone or combined with COX-2/PPARγ-targeting showed a significantly prolonged progression-free survival.[88] In metastatic melanoma, PPARγ expression may be a predicitive marker for response to biomodulatory stroma-targeted therapy. Regarding primary melanoma, COX-2 expression indicates an increased risk of tumor recurrence.

In order to circumvent the side-effect of chemotherapeutic drugs Wang et al. synthesized a conjugate of the PPAR ligand DHA and the anticancer agent doxorubicin, which deliver the chemotherapeutic agent specifically to tumor tissue.[89] In vitro and in experimental animal tumor models the created DHA-doxorubicin conjugate was significantly more efficacious than free doxorubicin. An other group analysed in a recently published phase I study the maximum tolerated dose, dose-limiting toxicity and pharmacokinetics of weekly DHA-paclitaxel in resistant solid tumor malignancies.[90] DHA-paclitaxel administered weekly to a maximum dose of 600 mg/m^2 was well-tolerated and provided stable disease for 16 weeks in a patient with melanoma. In addition to this, compared with the respectively chemotherapeutic agent alone, the combined conjugates DHA-doxorubicin and DHA-paclitaxel were much less toxic.[89-91]

Taken together, further investigations have to identify which PPAR ligands might be a new antimelanoma drug and might provide the initial impetus for coming clinical trials in melanoma treatment.

Conclusions

PPARs represent a major research target for the understanding and treatment of many skin diseases. Meanwhile a large number of PPAR ligands (i.e., long-chain fatty acids, thiazolidinediones, fibrates) have been identified. Some of them are already registered and clinically used for other diseases. Knowing that the route from identification to registration of drugs is long and expensive, drugs already registrated for the treatment of one disease but potentially effective for others are of high interest. The present review summerizes potential pharmaceutical targets to use PPAR ligands in the field of dermatology. Further in vitro and vivo studies followed by clinical trials are needed to validate the possible role of PPAR ligands to improve treatment of various dermatologic diseases.

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