# PPARdelta in Inflammatory Skin Diseases

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Peroxisome proliferator-activated receptors (PPARs) are nuclear hormone receptors expressed in the skin. Three PPAR isotypes, α (NRC1C1), β or δ (NRC1C2) and γ (NRC1C3), have been identified. After activation through ligand binding, PPARs heterodimerize with the 9-cis-retinoic acid receptor (RXR), another nuclear hormone receptor, to bind to specific PPAR-responsive elements in regulatory regions of target genes mainly involved in organogenesis, cell proliferation, cell differentiation, inflammation and metabolism of lipids or carbohydrates. Endogenous PPAR ligands are fatty acids and fatty acid metabolites. In past years, much emphasis has been given to PPARα and γ in skin diseases. PPARβ/δ is the least studied PPAR family member in the skin despite its key role in several important pathways regulating inflammation, keratinocyte proliferation and differentiation, metabolism and the oxidative stress response.

Keywords: PPAR ; atopic dermatitis ; psoriasis ; metabolic reprograming ; glucose ; fatty acids

## 1. PPARdelta: The Least Studied PPAR Isoform

Peroxisome proliferator-activated receptors (PPARs) are transcription factors belonging to nuclear hormone receptor superfamily. Three PPAR isotypes, α (NRC1C1), β or δ (NRC1C2) and γ (NRC1C3), have been identified in mammals (henceforth, we refer to the β/δ isoform simply as PPARδ). After activation through ligand binding, PPARs heterodimerize with the 9-cis-retinoic acid receptor (RXR), another nuclear hormone receptor, to bind to specific PPAR-responsive elements in regulatory regions of target genes, mainly involved in organogenesis, cell proliferation, cell differentiation, inflammation and metabolism of lipids or carbohydrates. Endogenous PPAR ligands are fatty acids and fatty acid metabolites.

PPARδ is ubiquitously expressed in murine tissues with highest expression in liver, muscle, adipose tissue, placenta, small intestine and skin. PPARδ is expressed twofold, 10-fold and 30-fold more in mouse keratinocytes (KCs) compared to mouse liver, quadriceps muscle and thymus, respectively. In most tissues, PPARδ localizes to the nuclear fraction of cells and is hardly detectable in the cytoplasm [1]. In humans, PPARδ mRNA and protein are highly abundant in the thyroid gland and placenta whereas high amounts of mRNA and moderate amounts of protein are detected in the cerebral cortex, skin and esophagus. Of note, inconsistency between protein and RNA levels of PPARδ has been observed in many human tissues and cell types (https://www.proteinatlas.org/ENSG00000112033-PPARD/tissue, accessed on 7 July 2021). There are five human and mouse PPARδ isoforms generated by alternative splicing, which is a mechanism potentially involved in PPARδ regulation, as some PPARδ splice isoforms exhibit reduced translation efficiency [2][3].

The ligand-binding pockets of PPARs have a distinct three-armed T shape, which allows not only straight fatty acids to bind them, but also ligands with multiple branches such as phospholipids and synthetic fibrates. The ligand-binding pocket of PPARδ is smaller than that of PPARγ or PPARα, which limits the binding of large ligands when compared to the other two PPAR isoforms [4]. PPARδ is activated by several endogenous ligands including certain long chain fatty acids (regardless of saturation status), dihomo-γ-linolenic acid, eicosapentaenoic acid, 15(S)-hydroxyeicosatetraenoic acid (HETE), and arachidonic acid, with affinities in the low micromolar range (**Table 1**). Supraphysiological doses of 8(S)-, 12(S)-, 12(R)-, and 15(S)-HETE efficiently activate PPARδ. 13(S)-hydroxyoctadecadienoic acid (HODE) is considered as weak PPARδ activator [5][6]. Controversial results have been found for prostacyclin (PGI2) and all-trans retinoic acid [7][8]. It has also been reported that 4-hydroxynonenal (4-HNE) and 4-hydroxydodecadienal (4-HDDE), the peroxidation products of polyunsaturated fatty acids, can activate PPARδ, although the mechanism remains unknown [9][10]. Synthetic PPARδ ligands include GW501516, GW0742 and L165041, which preferentially activate PPARδ as compared to PPARα or PPARγ [6]. Recently, 27 new synthetic PPARδ agonists (13 with low nanomolar $EC_{50}$ values) have been discovered [11]. However, it is important to stress that preferential ligand does not mean exclusive ligand and that supraphysiological doses of any of the PPARδ ligands will activate other PPAR isoforms, and the same is true for all PPAR isoforms. For example, bezafibrate, which is known as a PPARα ligand, activates all three PPARs at concentrations ranging from 55 to 110 μM [12]. In the absence of ligand binding, the heterodimer PPARδ-RXR is associated with corepressors and histone

deacetylases (HDACs), which inhibit its transcriptional activity. After ligand binding, PPARδ undergoes conformational changes that induce the release of the corepressors and allow it to bind coactivators [7].

**Table 1.** PPARδ potential endogenous ligands.

| Compounds | Weak Ligands | Ligands |
|---|---|---|
| ω3-PUFA | α-Linolenic acid C18:3 | EPA C20:5 |
| | γ-Linolenic acid C18:3 | |
| | Dihomo-γ-linolenic acid | |
| | DHA C22:6 | |
| ω6-PUFA | Linoleic acid C18:2 | |
| | Arachidonic acid C20:4 | |
| ω9-MUFA | Palmitoleic acid C16:1 | Oleic acid C18:1 |
| | Elaidic acid C18:1 | |
| | Erucic acid C22:1 | |
| | Nervonic acid C24:1 | |
| Saturated fatty acids | Myristic acid C14:0 | Arachidic acid C20:0 |
| | Palmitic acid C16:0 | |
| | Stearic acid C18:0 | |
| | Behenic acid C22:0 | |
| Eicosanoids | 5-HpETE | 5(S)-HETE |
| | 8(S)-HETE | 15(R)HpETE |
| | 15(S)HpETE | 15(R)-HETE |
| | 15(S)-HETE | 12-HETE |
| | 12-HpETE | LTB4 |
| | LTA4 | LTC4 |
| | 9(R)-HODE | 9(S)-HODE |
| | 12-HpODE | 5,6-diHETE |
| | 13(S)-HODE | |
| | 5,15-di-HpETE | |
| Prostaglandins | PGA2 | PGF1α |
| | PGB1 | |
| | PGB2 | |
| | PGD1 | |
| | PGD2 | |
| | PGD3 | |
| | PGF2α | |
| | PGF3α | |
| | PGI2 | |
| Lipoxins | | LXA4 |
| 4-Hydroxyalkenals | 4-HDDE | |

Adapted from [8]. DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; 4-HDDE; 4-hydroxydodecadienal; HETE: hydroxyeicosatetraenoic acid; HODE: hydroxyoctadecadienoic acid; LT: leukotriene; LX: lipoxin; PG: prostaglandin.

The transcriptional activity of PPARδ is modulated by several factors, which are not well characterized but include post-translational modifications such as phosphorylation. Epidermal growth factor receptor (EGFR) has been recently shown to induce PPARδ phosphorylation at Y108 in response to epidermal growth factor (EGF) [13]. Although PPARδ contains several putative phosphorylation sites (Y108, T252, T253, T256), (https://www.phosphosite.org/proteinAction.action?id=24004&showAllSites=true (accessed on 9 May 2021)) [14], little is known about phosphoregulation of PPARδ, in contrast to PPARα and PPARγ. Both cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA) activators increase the ligand-activated and basal activity of PPARδ and could be upstream signals that commit PPARδ to the regulation of glucose and lipid metabolism [14]. In contrast, PPARδ can also be sumoylated at K104, which inhibits its activity [14]. Desumoylation of PPARδ by small ubiquitin-like modifier (SUMO)-specific protease 2 (SENP2) promotes the transcriptional activity of PPARδ, which, in turn, upregulates fatty acid oxidation by enhancing the expression of long-chain-fatty-acid–CoA ligase 1 (ACSL1), carnitine palmitoyltransferase Ib (CPT1b) and mitochondrial uncoupling protein 3 (UCP3) in muscles of mice fed a high fat diet [15]. Moreover, PPARδ contains several ubiquitylation sites, which suggests a potential role of ubiquitin–proteosome degradation in the regulation of its cellular turnover (https://www.phosphosite.org/proteinAction.action?id=24004&showAllSites=true (accessed on 9 May 2021)). Degradation of PPARδ via the proteasome might prevent its accumulation in the nucleus and thereby moderate its cellular activity [16]. In line with this, overexpression of PPARδ in fibroblasts leads to its polyubiquitylation and rapid degradation, a process partially prevented by exposure to the PPARδ synthetic ligand GW501516 [17].

PPARs can also engage in transrepression of other transcription factors. Although transrepression between nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), activator protein 1 (AP-1), CCAAT-enhancer-binding protein (C/EBP), signal transducer and activator of transcription (STAT) and nuclear factor of activated T-cells (NF-AT) has been well characterized for PPARα and PPARγ, little is known about transrepression in the context of PPARδ [18][19]. L-165041 is a PPARδ ligand that is less potent and selective than GW501516, yet it promotes the binding of PPARδ to the p65 subunit of NF-κB exerting anti-inflammatory effects [5][20]. Moreover, in the absence of ligand, PPARδ binds directly to the transcription factor B-cell lymphoma 6 (BCL-6), leading to increased expression of proinflammatory cytokines. Indeed, BCL-6 is a transcription factor repressing the expression of various inflammatory genes via direct binding to their promoters or via inhibition of the transcription of nucleotide-binding oligomerization domain-like receptor (NOD)-like receptor family pyrin domain containing 3 (NLRP3) [21][22]. Binding of PPARδ to an agonist disrupts the PPARδ-BCL-6 complex, thus reversing the transcriptional repression of inflammatory genes [23]. Thus, ligand binding to PPARδ alleviates inflammation by enhancing its binding to NF-kB, hence neutralizing the transcriptional activity of NF-kB and/or the release of the anti-inflammatory transcription factor BCL-6. However, PPARδ has also been shown to bind to the N-terminal part of p65 in the absence of exogenous ligand [5]. Therefore, the pro- vs. anti-inflammatory role of PPARδ might be context- and ligand-dependent. Moreover, conformational changes experienced by PPARδ after ligand binding might potentially strengthen or weaken the affinity of PPARδ to p65; however, this has not been studied to date.

## 2. PPARdelta in Psoriasis and Atopic Dermatitis

Atopic dermatitis and psoriasis are two chronic and pruritic inflammatory skin diseases exhibiting pathophysiological commonalities, including impaired epidermal barrier function, immune hyper-responsiveness, and local and systemic symptoms modulated by environmental factors such as the skin microbiome and stress. Moreover, both diseases are associated with a major genetic risk factor, i.e., Filaggrin (*FLG*) loss-of-function mutations in atopic dermatitis and the HLA-Cw0602 allele in psoriasis vulgaris [24][25]. Furthermore, in both atopic dermatitis and psoriasis patients, nonlesional and lesional skin coexists, but the mechanism of transition from the non-affected to the affected condition remains unclear. Atopic dermatitis is one of the most common inflammatory skin diseases worldwide and characterized by skin features such as erythematous and papulovesicular eruptions with oozing, crusting and pruritus as well as associated systemic signs such as food allergies, allergic asthma and rhinitis, anxiety and sleep disorders. At the cellular level, atopic dermatitis is characterized by (a) the complex interplay between impaired epidermal barrier function owing to altered lipid composition of the stratum corneum lipid matrix i.e., a reduction in the chain length of structural lipids (fatty acids and ceramides), (b) a complex Th2-driven inflammation, (c) skin infiltration by eosinophils, basophils and inflammatory dendritic cells, and (d) an altered skin microbiota [24][26][27][28][29][30][31][32][33]. In psoriasis vulgaris, genetic risk factors predominantly affect innate immunity, and to some extent adaptive immunity (IL12p/IL-23R axis, Th1, Th17 cells). Similarly to atopic dermatitis, skin immunological abnormalities in psoriasis are complex and associated with comorbidities (e.g., arthritis and cardiovascular manifestations), pointing to a systemic immune hyper-responsiveness [25][31][34][35][36][37].

PPARδ is expressed in all skin cell types, including KCs, fibroblasts, sebocytes, hair follicle cells, melanocytes and Langerhans cells [19][38][39][40]. PPARδ is the predominant isoform in human KCs and is expressed throughout all epidermal layers [41][42]. Activation of PPARδ with synthetic ligands promotes the expression of human KC differentiation markers such as involucrin (*INV*) and transglutaminase 1 (*TGM1*) [42]. Although there is consensus on the pro-differentiative effects of PPARδ ligands and PPARδ activation in KCs, the effects on KC proliferation are more controversial, with studies showing reduced [42] or enhanced [43] KC proliferation after treatment with the PPARδ ligand L-165041 or GW-501516. Treatment of human KCs with L-165041 gave opposite outcomes in two distinct studies [43][42]. Yet, the use of different treatment regimens of L-165041, i.e., 0.05 μM for 3 days [42] and 1 μM for 7 days [43], might have been responsible for these divergent results, for example by inducing the recruitment of different cofactors and thus engaging PPARδ in different metabolic pathways. Moreover, the direct effects of ligands should not be underestimated because the use of PPARδ siRNA to test the requirement for PPARδ in the cellular response was not carried out in either studies [43][42]. In line with this, L-165041 can activate other PPAR isoforms, i.e., PPARα, PPARγ1 and PPARγ2 at doses as low as 0.05 μM [42]. This underscores that PPAR ligands can exert receptor-independent effects, that metabolic effects might vary with ligand concentrations (e.g., U- or bell-curves), and that the relative contribution of other PPAR isoforms after treatment with ligands might significantly influence experimental results, hence stressing the need for cautious interpretation of data [27]. Human KCs infected with a lentivirus containing an RNAi sequence directed toward PPARδ displayed reduced proliferative capacity, suggesting that PPARδ promotes, rather than dampens, proliferation of human KCs [43]. However, it is also possible that PPARδ exerts both proliferative and differentiative functions according to the cellular context, i.e., basal cells (early KCs, progenitor and stem cells) or suprabasal cells (differentiated cells). As in other cell types, PPARδ is likely a master regulator of fatty acid metabolism in KCs by increasing the uptake of long-chain fatty acids via upregulation of CD36 and fatty acid β-oxidation [42] (**Table 2**). However, the role of PPARδ in epidermal lipid and glucose metabolism remains under-investigated. Interestingly, the PPARδ target genes in KCs are not identical to those in other organs and cell types (**Table 2**), suggesting PPARδ has specific cellular functions in the epidermis.

**Table 2.** PPARδ target genes and associated pathways in keratinocytes.

| | Upregulated | Downregulated |
|---|---|---|
| **Fatty acid metabolism** | **FABP5** | **LASS6** |
| | **FABP7** | **GPD1L** |
| | **ACADVL** | **PRKAB2** |
| | **ACOX1** | **CHPT1** |
| | **CD36** | |
| | **ALOX12B** | |
| | **LDLR** | |
| | **PLA2G3** | |
| | **ECHB** | |
| | **OACT5** | |
| | **BDH1** | |
| | **GDPD3** | |
| | **CRABP2** | |
| | **GM2A** | |

| | Upregulated | Downregulated |
|---|---|---|
| **Cholesterol metabolism** | **HMGCS1** | |
| | **HMGCR** | |
| | **MVD** | |
| | **CYP51** | |
| | **SQLE** | |
| | **FDPS** | |
| | **LSS** | |
| | **FDFT1** | |
| | **DHC7** | |
| **KC proliferation** | | **EGFR** |
| | | **EPS15** |
| | | **EPS8** |
| | | **MCC** |
| | | **RBL2** |
| | **HB-EGF** | **CCNG1** |
| | | **DUSP3** |
| | | **PDGFRA** |
| | | **PDGFC** |
| | | **CDKN1C** |
| **KC differentiation** | **INV** | **DCN** |
| | **TGM1** | **KRT15** |
| | **TGM3** | **DUSP3** |
| | **S100A8** | |
| | **S100A9** | |
| | **S100A16** | |
| | **KRT6B** | |
| | **KRT16** | |
| | **KRT17** | |
| | **KRT75** | |
| | **SPRR1B** | |
| | **CNFN** | |
| | **EHF** | |
| **KC apoptosis** | **CIDEA** | |

| | Upregulated | Downregulated |
|---|---|---|
| **Inflammation** | **MMP9** | **TGFBR2** |
| | **IL1F9** | **TGFBR3** |
| | **IL1F5** | **LIFR** |
| | **IL1B** | **IL1R1** |
| | **IL1F6** | |
| | **IL1F8** | |
| | **ILA** | |
| | **IL1RA** | |
| | **IL18** | |
| | **IL17** | |
| | **IL23A** | |
| | **IL22** | |
| | **STAT3** | |
| **Glucose metabolism** | **PDK1** | **PDK4** |
| **Oxidative stress** | **SOD2** | |
| | **CAT** | |
| | **ABCC3** | |
| **Other** | **HAS3** | **RBL2** |
| | **GGH** | **AXL** |
| | **UCK2** | **RHOC** |
| | **ATP10B** | **TTC3** |
| | **CCNB1** | **LFNG** |
| | **MAPK13** | **FXR1** |
| | **CCNB2** | **FBLN1** |
| | **GSPT1** | **GAB2** |
| | **XPC** | |
| | | **PIK3IP1** |
| **Unknown** | **AKR1B1** | **SERINC1** |
| | **ATP12A** | **EID1** |
| | **ACPP** | **KLF6** |
| | **MAP4K4** | **RAI14** |
| | **MREG** | **MTCP1** |
| | **FGFBP1** | **REEP5** |
| | **ARL8B** | **NENF** |
| | **GAS7** | |
| | **CD81** | |
| | **CCDC50** | |
| | **TACC1** | |
| | | **OSR2** |

ABCC3: ATP binding cassette subfamily C member 3; ACAD(V)L: (very) long-chain specific acyl-CoA dehydrogenase, mitochondrial; ACOX1: acyl-CoA oxidase 1; ACPP (ACP3): acid phosphatase 3; AKR1B1: aldo-keto reductase family 1 member B; ALOX: lipoxygenase; ATP10B: ATPase phospholipid transporting 10B; ATP12A: ATPase H+/K+ transporting non-gastric alpha2 subunit; ARL8B: ADP ribosylation factor like GTPase 8B; AXL: AXL receptor tyrosine kinase; BDH1: 3-hydroxybutyrate dehydrogenase 1; CAT: catalase; CCDC50: coiled-coil domain containing 50; CCN: cyclin; CD: cluster of differentiation; CDKN1C: cyclin dependent kinase inhibitor 1C; CHPT1: choline C phosphotransferase 1; CIDEA: cell death inducing DFFA like effector A; CNFN: cornifelin; CRABP2: cellular retinoic acid binding protein 2; CYP51: lanosterol 14α-demethylase; DCN: decorin; DHC7 (DNAH1): dynein axonemal heavy chain 1; DUSP3: dual specificity phosphatase 3; ECHB (HADHB): hydroxyacyl-CoA dehydrogenase trifunctional multienzyme complex subunit beta; EGFR: epidermal growth factor receptor; EHF: ETS homologous factor; EID1: EP300 interacting inhibitor of differentiation 1; EPS: epidermal growth factor receptor pathway substrate; FABP: fatty acid binding protein; FBLN1: fibulin 1; FDFT1: farnesyl-diphosphate farnesyltransferase 1; FDPS: farnesyl diphosphate synthase; FGFBP1: fibroblast growth factor binding protein 1; FXR1: FMR1 autosomal homolog 1; GAB2: GRB2 associated binding protein 2; GAS7: growth arrest specific 7; GDPD3: glycerophosphodiester phosphodiesterase domain containing 3; GGH: gamma-glutamyl hydrolase; GM2A: GM2 ganglioside activator; GPD1L: glycerol-3-phosphate dehydrogenase 1 like; GSPT1: G1 to S phase transition 1; HAS3: hyaluronan synthase 3; HB-EGF: heparin-binding EGF-like growth factor; HMGCR: 3-hydroxy-3-methylglutaryl-CoA reductase; HMGCS1: 3-hydroxy-3-methylglutaryl-CoA synthase 1; IL: interleukin; INV: involucrin; KLF6: kruppel like factor 6; KRT: keratin; LASS6 (CERS6): ceramide synthase 6; LDLR: low density lipoprotein receptor; LFNG: LFNG O-fucosylpeptide 3-beta-N-acetylglucosaminyltransferase; LIFR: LIF receptor subunit alpha; LSS: lanosterol synthase; MAP4K4: mitogen-activated protein kinase kinase kinase kinase 4; MAPK13: mitogen-activated protein kinase 13; MCC: MCC regulator of WNT signaling pathway; MMP9: matrix metalloproteinase 9; MREG: melanoregulin; MTCP1: mature T cell proliferation 1; MVD: mevalonate diphosphate decarboxylase; NENF: neudesin neurotrophic factor; OACT5 (LPCAT3): lysophosphatidylcholine acyltransferase 3; OSR2: odd-skipped related transcription factor 2; PDGFC: platelet derived growth factor C; PDGFRA: platelet derived growth factor receptor alpha; PDK: pyruvate dehydrogenase kinase; PIK3IP1: phosphoinositide-3-kinase interacting protein 1; PLA2G3: phospholipase A2 group III; PRKAB2: protein kinase AMP-activated non-catalytic subunit beta 2; RAI14: retinoic acid induced 14; RBL2: RB transcriptional corepressor like 2; REEP5: receptor accessory protein 5; RHOC: ras homolog family member C; S100A: S100 calcium-binding protein A; SERINC1: serine incorporator 1; SOD2: superoxide dismutase 2; SPRR1B: small proline rich protein 1B; SQLE: squalene epoxidase; STAT: signal transducer and activator of transcription; TACC1: transforming acidic coiled-coil containing protein 1; TGFBR: transforming growth factor beta receptor; TGM: transglutaminase; TTC3: tetratricopeptide repeat domain 3; UCK2: uridine-cytidine kinase 2; XPC: XPC complex subunit, DNA damage recognition and repair factor.

The *PPARD*/*Ppard* gene is upregulated in lesional skin of patients with psoriasis vulgaris [5][43][44][45][46][47][48] and of mouse models of psoriasis [46][47]. However, although *PPARD* has been identified as a putative pathogenic gene in psoriasis [48], variants at the *PPARD* genomic locus have not been associated with psoriasis. In psoriatic plaques, PPARδ accumulates in KC nuclei in all epidermal layers [5]; however, subcellularly, PPARδ is found both in the cytoplasm and nucleus of KCs in the basal layer and in the stratum spinosum, whereas it is strictly found in nuclei in KCs in the stratum granulosum [5][47]. This suggests that PPARδ is constitutively activated by endogenous ligands in granular KCs of the epidermis in patients with psoriatic lesions [47]. Accordingly, endogenous PPARδ ligands can be produced in psoriatic lesions from the oxidation of arachidonic acid via ALOX8 (mouse) or ALOX12 (mouse and human) [47][49], two enzymes located in the stratum granulosum [49][50][51]. FABP5 is a fatty acid-binding protein expressed in the epidermis and has been shown to deliver endogenous lipid ligands to PPARδ in KC nuclei and to be a PPARδ target gene [52]. The expression of FABP5 parallels that of PPARδ at both the mRNA and protein levels in psoriasis [5][46]. Thus, in the suprabasal epidermis of psoriatic lesions, it is likely that PPARδ is constitutively activated by endogenous ligands such as arachidonic acid or its derivatives (eicosanoids), which are transported by FABP5 to the nucleus of granular KCs to promote PPARδ–mediated KC terminal differentiation and lipid β-oxidation. Specific overexpression and activation of human PPARδ in suprabasal mouse epidermis has been achieved by generating transgenic mice expressing a Cyp1A1-driven expression of human *PPARD* in KCs followed by topical treatment with the PPARδ agonist GW501516 [45]. Interestingly, these mice developed psoriasis-like inflammation associated with an increased Th17 immune response [45]. In this model, sustained activation of the STAT3 pathway is critically involved in the development of psoriasis-like disease [45]. The constitutive activation of PPARδ in suprabasal epidermis not only promotes terminal KC differentiation but also the production, in KCs, of IL-36 and the pleiotropic pro-inflammatory cytokine IL-1β. The latter can contribute to the activation of skin dendritic cells, which can in turn, skew naïve T cells toward a Th17 phenotype [45]. Moreover, suprabasal mouse KCs overexpressing the constitutively activated human PPARδ probably secrete soluble factors able to trigger the proliferation of basal KCs [45]. In addition, in psoriatic plaques, some PPARδ localize to nuclei in basal KCs to potentially sustain KC proliferation [5][47]. In line with this, previous work suggested that upregulation of PPARδ in the epidermis of psoriatic lesions might contribute to KC hyperproliferation via the upregulation of heparin-binding EGF-like growth factor

(HB-EGF) at the mRNA and protein levels [43]. HB-EGF is a ligand that activates EGFR and is expressed in the basal layer of the epidermis, where it has been shown to accelerate wound healing [53]. This might be relevant for psoriasis because disease flares can be induced by physical trauma (the isomorphic or Koebner phenomenon) among other causes. Pioneering work on the pathogenesis of psoriasis showed increased levels of antimicrobial peptides in psoriatic skin breaks the innate tolerance to self-DNA which ultimately drives autoimmunity [54]. Moreover, human genomic DNA fragments enhance *TNFA* and *HBEGF* expression as well as KC proliferation, hence mimicking the KC phenotype in psoriatic skin lesions [55]. Thus, we can speculate that PPARδ in the basal epidermis of psoriatic plaques sustains KC proliferation via mechanisms involving HB-EGF. NF-kB has been shown to inhibit PPARδ-dependent transactivation. However, in lesional psoriasis, p65 NF-kB is sequestered in the cytoplasm of basal KCs, which might allow PPARδ to exert its transcriptional regulation on various genes, including those involved in KC proliferation [5].

PPARδ is upregulated in the epidermis of lesional atopic dermatitis when compared to non-lesional skin but to a lesser extent than in psoriatic lesions [43]. The expression of *FABP5* parallels that of PPARδ in psoriasis and atopic dermatitis [43][56]. Notably, the expression of *Ppard* and *Fabp5* is markedly increased in the epidermis of mouse models of lesional atopic dermatitis [57][58]. Similar to psoriasis, FABP5 is mainly localized to the nuclei of suprabasal KCs, suggesting efficient local generation of PPARδ ligands to sustain the activation of PPARδ [57]. Interestingly, the amounts of arachidonic acid, PGF2α and 5-HETE (PPARδ endogenous ligands) are increased in lesional skin of atopic dermatitis patients when compared to healthy skin [59]. The increased cleavage of membrane phospholipids via cPLA2 in the stratum granulosum can significantly contribute to the accumulation of arachidonic acid and its derivatives in lesional atopic dermatitis skin as well as in psoriatic lesions [60][61][62]. The role of PPARδ has been less investigated in atopic dermatitis than in psoriasis. However, in both diseases, PPARδ might induce KC hyperproliferation, enhance differentiation and contribute to inflammatory processes.

However, PPARδ can also be envisaged as a key regulator of metabolism, especially in the metabolic shift toward anaerobic glycolysis that has been recently evidenced in psoriatic and atopic lesions [57][63][64]. The production of lactate is largely increased in the epidermis of flaky tail mice and mice treated with MC903, two mouse models of lesional atopic dermatitis [57] and of mice treated with imiquimod, a mouse model of psoriasis [65]. Interestingly, the PPARδ ligand GW610742, when orally administered to *ob/ob* mice, induces lactate accumulation in the liver [66]. Indeed, PPARδ has been shown to regulate the expression of key enzymes involved in glucose metabolism, including in KCs (**Table 2**) [67][68][69]. PPARδ can promote anaerobic glycolysis by upregulating PDK, an enzyme that inactivates pyruvate dehydrogenase (PDH) via phosphorylation. PDH is the rate-limiting enzyme involved in pyruvate uptake in mitochondria, which ultimately favors oxidative phosphorylation [70]. Thus, inactivation of PDH by PPARδ-induced PDK inhibits pyruvate uptake in mitochondria, which, in turn, promotes anaerobic glycolysis [71]. In the epidermis of flaky tail mice, there is a shift toward anaerobic glycolysis associated with an enhanced PPARδ pathway including increased PDK1. In line with this, mitochondrial function is not enhanced in the epidermis of flaky tail mice despite a dramatic need for energy to sustain forced KC proliferation and to dampen inflammation [57]. These results are in line with previous work showing that PPARδ antagonism favors mitochondrial function [72].

PPARδ promotes β-oxidation of fatty acids in all cell types, including KCs (**Table 2**) [69][73][74]. In flaky tail mice, peroxisomal β-oxidation is upregulated when compared to that of healthy mice, with marked increases in the mRNA, protein and activity levels of ACOX1 [57], a well-known PPARδ downstream target [73][74]. This profile has been observed in another mouse model of lesional atopic dermatitis, i.e., mice topically treated with MC903 [57]. This treatment is associated with decreased proportions of very-long chain fatty acids and ceramides, especially with 24 and 26 carbons [57], as observed in the epidermis of patients with lesional atopic dermatitis [75]. Interestingly, C24 and C26 fatty acids are exclusively oxidized in peroxisomes via ACOX1 [76][77]. Thus, the upregulation of PPARδ in the epidermis of patients with lesional atopic dermatitis might promote peroxisomal β-oxidation of very- and ultra-long-chain fatty acids and ceramides, hence significantly contributing to disease pathogenesis. Indeed, the efficacy of the stratum corneum barrier depends, to a large part, on the lipid composition of the lipid matrix surrounding the corneocytes, which consists of more than 50% fatty acids with 24 and 26 carbons. Interestingly, the proportion of very-long-chain ceramides is also decreased in the epidermis of psoriatic lesions [78] and is associated with increased ACOX1 [57] and PPARδ (see above), thus corroborating the key role of the PPARδ pathway in lipid abnormalities in both lesional atopic dermatitis and psoriasis. In contrast to lesional AD [57], mitochondrial β-oxidation might be increased in psoriasis as suggested by previous work [27] and might further contribute to lipid abnormities.

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