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Eicosanoids in Skin Inflammation

Anna Nicolaou*

School of Pharmacy and Centre for Skin Sciences, School of Life Sciences, University of
Bradford, Richmond Road, Bradford BD7 1DP, UK.

*correspondence to: Email: a.nicolaou@bradford.ac.uk;

Tel: +44 (0) 1274 234717;

Fax: +44 (0) 1274 235600

Summary

Eicosanoids play an integral part in homeostatic mechanisms related to skin health and structural integrity. They also mediate inflammatory events developed in response to environmental factors, such as exposure to ultraviolet radiation, and inflammatory and allergic disorders, including psoriasis and atopic dermatitis. This review article discusses biochemical aspects related to cutaneous eicosanoid metabolism, the contribution of these potent autacoids to skin inflammation and related conditions, and considers the importance of nutritional supplementation with bioactives such as omega-3 and omega-6 polyunsaturated fatty acids and plant-derived antioxidants as means of addressing skin health issues.

1. Introduction

Eicosanoids are produced by all cutaneous cell types and contribute to homeostatic processes and inflammatory responses associated with injury, allergy and other acute or chronic conditions [1-3]. Membrane phospholipid-esterified arachidonic acid (20:4n-6; AA) and the C20 polyunsaturated fatty acids (PUFA) dihomo- γ -linolenic acid (DGLA; 20:3n-6) and eicosapentaenoic acid (EPA; 20:5n-3) are mobilised by phospholipases and serve as precursors to various eicosanoids that are formed by cutaneous cyclooxygenase (COX) and terminal prostanoid synthases (PGS), lipoxygenase (LOX) and cytochrome P450 (CYP) enzymes. Eicosanoid-like molecules are also produced through non-enzymatic oxidations, whilst other n-6 and n-3 PUFA including linoleic acid (LA; 18:2n-6) and docosahexaenoic acid (DHA; 22:6n-3) can give rise to analogous lipid mediators [4, 5] (Figure 1).

Skin is considered the largest organs of the body and constitutes a physical barrier protecting it from injury, infection, water and electrolyte loss, as well as being an important player of the immune system [6]. It has a multilayered structure that supports the formation of a highly-keratinized outer epidermal permeability barrier, whilst the epidermis and dermis host a number of primary cells including epidermal keratinocytes, melanocytes, and Langerhans cells, as well as dermal fibroblasts, mast cells, and infiltrating leukocytes. Inflammation partakes in physiological mechanisms mediating skin healing and repair post injury, whilst it is a central feature in a number of dermatoses and underpins cancer development. Skin cells participating in these events produce eicosanoids in response to various stimuli and this can be influenced by dietary manipulation; therefore an in depth appreciation of these potent lipid mediators of cutaneous inflammation is of great importance.

This article aims to review our current understanding of cutaneous eicosanoid production and their contribution to inflammatory conditions, and will discuss systemic and

local interventions that have been considered as means of manipulating lipid mediator production with a view to improve skin health and develop chemopreventive regimes.

2. Cutaneous Eicosanoid Biology

Fatty acids are crucial for skin structure and function, as shown by the seminal studies of Burr et al [7] that demonstrated its dependence on systemically provided essential fatty acids. LA constitutes approximately 12% of cutaneous fatty acids and is pivotal for the integrity of the epidermal barrier [8-10]. Furthermore, epidermal keratinocytes are characterized by lack of $\Delta 5$ and $\Delta 6$ desaturase activity [11] and rely on systemic provision of long chain PUFA such as AA, DHA and EPA that, collectively, account for no more than 5% of total fatty acids [12]. Although their precursors are found at such low levels, PUFA-derived prostanoids and hydroxy-fatty acids are important for skin physiology and homeostasis [9, 13, 14].

2.1. Phospholipases

Phospholipase A₂ (PLA₂) is the principle lipolytic enzyme providing AA and other PUFA for eicosanoid biosynthesis [15]. Of the many isoforms, the cytosolic PLA₂ (cPLA₂) is considered the main enzyme mediating the release of AA for cutaneous eicosanoids with its activity and expression found induced in conditions characterized by oxidative stress (e.g. sunburn) [16]. The secretory PLA₂ (sPLA₂) has also been found in keratinocytes and sites of cutaneous inflammation (e.g. psoriasis) [17, 18]. Finally, phosphatidylinositol (PI)- specific phospholipase C (PLC) that releases diacylglycerol (DAG) which can be further metabolised by lipases to generate AA and in this way potentially contribute to skin eicosanoids, has also been reported to be involved in certain inflammatory conditions (e.g. psoriasis) [19, 20].

2.2. Cyclooxygenase-derived mediators

Cyclooxygenase isoforms, i.e. the constitutive COX-1 and inducible COX-2, convert AA to the unstable intermediate PGH₂ that is further isomerized to prostaglandins, prostacyclin or thromboxanes (prostanoids) depending on the prevalence of the corresponding terminal prostanoid synthases. EPA and DGLA are also metabolized by COX and generate a range of prostanoids (Figure 1). Most mammalian cutaneous cells express COX-1 and -2, and studies on human and animal skin have shown the production of PGE₂, PGE₁, PGE₃, PGD₂, PGF_{2α}, PGI₂, and TXB₂ [13, 21, 22]. However, the exact prostanoid profile for each skin cell type, and the influence these mediators may have on transcellular metabolism and the overall skin function continues to be of interest.

PGE₂ is one of the main cutaneous eicosanoids produced by both epidermal keratinocytes and dermal fibroblasts. It exhibits potent pro-inflammatory and vasodilatory properties, promotes proliferation and modulates immunosuppression [22, 23]. These effects are mediated through G-protein coupled receptors EP1-4 expressed in all primary skin cells [24-27]. PGE₂ is formed via the cytosolic and microsomal PGE synthases (cPGES, mPGES-1 and mPGES-2) [28]. Interestingly, there is evident for linked expression of the inducible mPGES-1 and COX-2 isozymes demonstrating in skin cells the presence of an efficient system for increased PGE₂ production upon stimulation [29]. Furthermore, PGE₂ is involved in keratinocyte proliferation and differentiation, and this has direct consequences for the epidermal barrier function [25, 30, 31]. It has also been suggested that fibroblast-produced PGE₂ influences keratinocyte growth showing the cross-talk and biochemical support between skin layers [32, 33]. Finally, PGE₂ can act as keratinocyte chemoattractant and modulator of dermal fibroblasts, and in this way can facilitate wound healing [34, 35]. Recent reports suggest that epidermal melanocytes can also produce PGE₂ although the lack

of COX-2 protein expression in these cells may explain the relatively low levels observed [36, 37]. However, PGE₂ has a direct effect on melanocyte-mediated post-inflammatory pigimentary responses and melanocyte dendricity showing relevance to skin tanning [27, 38].

Langerhans cells and dermal mast cells are considered to be the principle producers of cutaneous PGD₂, a potent anti-proliferative and anti-inflammatory prostaglandin involved in immune and allergic responses [23, 39]. It exhibits its effects through the CRTH2 and DP receptors expressed in various skin cells, including keratinocytes [40, 41]. Recent studies have shown the production of PGD₂ by epidermal melanocytes [37]. Notably, Langerhans cells and mast cells express the hematopoietic PGD synthase (H-PGDS) isoform that responds to antigen stimulation [42], whilst melanocytes express the lipocalin PDGS (L-PGDS) isoform [37, 43] reflecting their neural crest origin. PGD₂ is precursor to the anti-inflammatory cyclopentanone prostaglandins PGJ₂, Δ^{12} -PGJ₂ and 15d-PGJ₂ that are formed through non-enzymatic hydrolysis [44]. Although Δ^{12} -PGJ₂ has been shown to exhibit anti-proliferative effects in epidermal cells in vitro [45], the formation of such potent electrophiles by skin cells has not yet been well documented.

PGF_{2 α} can be produced by the PGH₂ 9,11-endoperoxide reductase or from PGE₂ via 9-ketoreductase, whilst the epimeric form 9 α ,11 β -PGF₂ (11-epi-PGF_{2 α}) is formed from PGD₂ via 11-ketoreductase [46]. PGF_{2 α} has been found in whole skin and keratinocytes in culture [21, 22, 47] and has been linked to inflammation, immune responses, pigmentation and hair growth [27, 38, 48]. The effects of PGF_{2 α} are mediated through the FP receptor found expressed in epidermal cells and melanocytes [49-51]. Finally, prostacyclin (PGI₂; detected as 6-keto-PGF_{1 α}) and TXA₂ (detected as TXB₂) have been found in whole skin extracts and cultured cells in vitro, albeit at low concentrations and it is possible that they may also be products of vascular endothelial cell or derive from infiltrating leukocytes [21, 31]. IP and TP

receptors have been identified in keratinocytes and other skin cells [24, 52] and their prevalence has been linked to PGI₂ and TXA₂ signalling events accompanied cutaneous inflammatory and immune disorders [53, 54].

Cutaneous prostaglandins are catabolised through oxidation via the NAD⁺-dependent 15-ketoprostaglandin dehydrogenases (15-PGDH) followed by reduction through the Δ^{13} -15-ketoprostaglandin reductases [55]. The resulting 15-keto- and 13,14-dihydro-15-keto prostaglandins have substantially reduced biological activities. The enzymes and products of prostaglandin catabolism are ubiquitously found in human and animal cells [22, 56, 57].

2.3. *Lipoxygenase-derived mediators*

Lipoxygenase (LOX) activities are conventionally defined by their positional selectivity when oxygenating AA in a stereoselective manner [5, 58], although this classification system does not always reflect the isozyme complexity as suggested by phylogenetic studies [59]. Human and animal skin expresses 5-, 8-, 12- and 15-LOX activities producing an array of hydroxy-fatty acid derivatives of AA, LA, DGLA, EPA and DHA, including 12-HETE, 15-HETE, 13-HODE and 15-HETrE [22, 60-63].

5-LOX is activated by FLAP (5-lipoxygenase activating protein) to produce the unstable peroxide 5-hydroperoxy eicosatetraenoic acid (HPETE) from AA, that is quickly reduced to 5-eicosatetraenoic (HETE) acid and 5-oxo-eicosatetraenoic (ETE) acid [64], or dehydrated to leukotriene (LT) A₄, precursor to LTB₄. LTA₄ can be further conjugated to GSH and generate a series of peptido-leukotrienes, or, following transcellular metabolism, contribute to the formation of lipoxins (LX) [65]. Cutaneous 5-LOX activity is rather low and has been associated mainly with epidermal keratinocytes [66, 67], Langerhans cells [68, 69] and infiltrating leukocytes [65]. Interestingly, 5-LOX activity is increased when keratinocytes differentiate [70]. LT and 5-oxo-ETE are potent chemoattractants [64, 71] that can contribute

to cutaneous inflammation and allergy [72, 73], however, the actual formation of peptidoleukotrienes in human skin has been disputed [74].

12-LOX activity is mediated by the highly abundant cytosolic leukocyte-type 12-LOX, the microsomal platelet-type 12-LOX, and the unique to mammalian skin cells, 12*R*-LOX [75]. The epidermis-type lipoxygenase-3 (eLOX-3) is acting in sequence with 12*R*-LOX contributing to the terminal differentiation of keratinocytes and integrity of the epidermal barrier [76, 77]. 15-LOX activity is attributed to two isoforms: the reticulocyte-type 15-LOX-1 and epidermis-type 15-LOX-2. Interestingly, leukocyte-type 12-LOX can form both 12- and 15-HETE and has high homology to 15-LOX-1; therefore, these isozymes are frequently referred to as 12/15-LOX [59]. Finally, murine epidermis is expressing 8-LOX, a homologue of the inducible 15-LOX-2, that has not yet been found in human skin [78, 79].

12-HETE is a potent pro-inflammatory chemotactic mediator, produced by epidermal keratinocytes and dermal fibroblasts. The expression of 12-HETE binding sites in keratinocytes and Langerhans cells suggesting an active involvement in cutaneous wound healing and inflammatory disease [35]. It has also been suggested that dermal 15-HETE can inhibit epidermal 12-LOX activity [80], whilst the reciprocal regulation of 12-LOX and 15-LOX activities has been reported in human keratinocytes *in vitro* [81]. Furthermore, 15-HETE may dampen the infiltration of PMN and exercise further anti-inflammatory activities as biochemical precursor of lipoxins [65]. 15-LOX and its metabolites may also mediate anti-cancer and protective effects similarly to its homologous murine 8-LOX [82]. Anti-inflammatory and anti-proliferative activities have also been attributed to 13-HODE and 15-HETrE, 15-LOX-derived mediators of LA and DGLA respectively, that have also been found in human and animal skin [62, 83, 84]. Finally, 8, 9- and 11-HETE have also been detected in human skin, although their exact origin has not yet been fully elucidated [22, 62].

2.4. CYP-derived mediators

Skin cells express a number of CYP isoforms involved in drug and xenobiotic metabolism and production of omega-hydroxylated ceramides for the epidermal barrier [85]. Although some AA-specific mono-oxygenases have been identified in epidermal keratinocytes [86, 87], the overall contribution of CYP in cutaneous eicosanoid production remains to be explored. CYP-derived eicosanoids include *cis*-epoxyeicosatrienoic acids (EET), involved in vascular relaxation and angiogenesis, their biologically inactive dihydro- metabolites (DHET), various mid-chain HETE (e.g. 8-,9-11-,12-15-HETE), and ω -hydroxylated PUFA such as 20-HETE (reviewed in [5]). Furthermore, CYP isoforms express varied stereo- and regio-selectivity resulting in the formation of multiple AA mediators, including *R*-HETE species. It is therefore plausible that some of the HETE identified in the skin and cutaneous cells in vitro may be products of CYP-mediated reactions. EET have been identified in mouse skin cells [88] and 11,12- and 14,15-EET have been shown to play a part in the cornification of human and mouse keratinocytes [89].

2.5. Non-enzymatically produced eicosanoids

Free-radical induced lipid peroxidation can generate isoprostanes or racemic mixtures of hydroxy fatty acids [90]. The main feature of these reactions is the lack of stereoselectivity and the resulting products are regio- and stereo-isomers of their enzymatically-produced counterparts. Oxidative stress is a feature of many cutaneous conditions and the formation of isoprostanes has been reported in sunburn skin whilst racemic hydroxy-fatty acids have been identified in psoriatic skin [91, 92]. Therefore, elucidating the exact stereochemistry of the mediators involved in each case is needed in order to appreciate the origin and bioactivity of cutaneous eicosanoids.

3. Eicosanoids in cutaneous inflammatory diseases

Inflammation is a prominent feature in a number of acute and chronic skin diseases including psoriasis and atopic dermatitis, disorders arising from exposure to UVR radiation (sunlight or recreational use of sunbeds), as well as being an underpinning factor in skin cancer. Cutaneous eicosanoids have been shown to be actively engaged in many biochemical and cellular events involved in these conditions.

3.1. Psoriasis

Psoriasis is a relatively common chronic inflammatory and proliferative skin disease, with genetic and environmental aetiologies, that is characterized by abnormalities in skin lipids and increased production of inflammatory mediators [93, 94].

Studies have shown increased sPLA₂, cPLA₂ and PLC activities in psoriatic skin [17-19, 95]. 12-HETE is the predominant eicosanoid found greatly up-regulated in psoriasis, whilst increases in the levels of PGE₂ and PGF_{2α} are less prominent [3, 96] and 15-HETE is decreased in uninvolved psoriatic skin compared to healthy epidermis [97]. Chiral analysis has revealed the prevalence of 12*R*-HETE in psoriatic scales pointing at the involvement of 12*R*-LOX [75]. 13-(*R,S*)-HODE have also been found in psoriatic skin [98] suggesting not only an upregulation of LOX reactions but also the potential formation of racemic hydroxy-fatty acid mixtures due to oxidative stress, another feature of this disease [99]. Furthermore, the contribution of *R*-hydroxy-fatty acid producing CYP isoforms, cannot be excluded. CYP isozymes can mediate the oxidation of eicosanoids, as suggested by the co-localisation of COX-2, mPGES-1 and CYP4F8 in psoriatic lesions leading to oxidation of PGE₂ [100]. In the past there has been a strong interest in the role of 5-LOX-derived leukotrienes in psoriasis and other skin disorders [96, 101]. However, the low 5-LOX activity in epidermal keratinocytes indicates that these eicosanoids may be formed through transcellular pathways

involving dermally infiltrating neutrophils [102], a consequence of the high concentration of the 12-HETE, a potent chemotactic eicosanoid highly prevalent in psoriatic skin.

The eicosanoid pathway has also been of interest in developing therapeutic approaches for psoriasis. 15-HETE has shown potential as an anti-inflammatory agent, as supported by the improvement observed in a clinical study following its injection on psoriatic scales [103]. These properties of 15-HETE can be attributed to its ability to counteract the chemotactic potencies of 12-HETE and LTB₄ [80, 104], as well as acting as substrate for the formation of lipoxins through transcellular metabolism involving the neutrophil infiltrate [65]. Nutritional approaches with GLA, DGLA and EPA, as well as local application and intravenous administration of EPA have also been considered, aiming to reduce the prevalence of AA-derived HETE and increase the concentration of less inflammatory PUFA derivatives such as 15-HEPE and 15-HETrE [105-108]. Finally, there has been interest in developing specific 12-LOX and PLA₂ inhibitors as therapeutic agents for psoriasis [109, 110].

3.2. Atopic Dermatitis

Atopic dermatitis is a common chronic allergic inflammatory disease [111]. It is attributed to genetic and environmental factors, and is characterized by abnormal skin barrier formation; however, the exact aetiology of it is not clear [112]. Epidermal keratinocytes are considered actively involved in atopic and allergic contact dermatitis, both in terms of producing inflammatory mediators but also in their ability to respond to inflammatory and allergenic stimuli [113].

As in most cutaneous inflammatory conditions, atopic dermatitis is characterised by increased PLA₂ activity [114] with COX-derived prostanoids apparently more involved than LOX-derived mediators [115]; a similar profile also observed in contact dermatitis [26].

Although the involvement of 5-LOX and LTB₄ has been shown in animal models of atopic dermatitis [116], as discussed, it is likely that this can be attributed to dermal neutrophilic infiltrates. PGD₂ is one of the principle prostanoids involved in atopic dermatitis because of its immunomodulatory properties and the active role of Langerhans cells and mast cells (the main cutaneous courses of PGD₂) in this primarily immunological problem [21, 117]. Finally, the vasoactive PGI₂ and immunosuppressive PGE₂ have also been suggested to be actively involved [26, 53]. In vitro studies with GLA and DHA suggest that PUFA can alter the profile of eicosanoids produced by cutaneous immune cells and, in this way, improve atopic dermatitis [118].

3.3. Sunburn Response

Inflammation plays a central role in the development of sunburn, a cutaneous reaction to acute exposure to sunlight with eicosanoids involved in associated biochemical and cellular events [1]. Inflammation is also involved in other UVR-related cutaneous conditions including photosensitivity disorders, photoageing, and skin cancer [119-121].

Overall, sunburn is characterised by increased COX- and LOX-mediated eicosanoid production. Exposure of cells to UVR (primarily UVB 290-320nm but also UVA 320-400nm) generates reactive oxygen species and activates signalling cascades, transcription factors and gene expression [122]. UVR-induced oxidative stress stimulates the activity and expression of cPLA₂ in human and animal skin, and keratinocytes in vitro [16, 123]; UVR-mediated activation of PLC has also been reported [124]. Up-regulation of COX-2 occurs within 3-4 hours post UVR and results in increased production of PGE₂ and PGF_{2α} [22], whilst the observed reduction in PGD₂ levels has been attributed to migration of epidermal Langerhan cells [125]. Studies in animals skin cells suggest UVR-induced up-regulation of prostaglandin synthase and receptor mRNA expression [24], and the catabolism of

prostanoids may be temporarily reduced, as shown by studies reporting reduction in 15-PGDH mRNA and protein post UVR [126]. The expression of cutaneous 12-LOX and 15-LOX is also up-regulated following exposure to UVR with concomitant production of a range of mediators, including 8-, 9-, 11- 12- and 15-HETE, and 13-HODE [22, 62]. Not much is known about the effect of UVR on eicosanoid production by CYP, although a UVR-related effect should be anticipated as alluded to by report showing increased activity of a cutaneous CYP isoform involved in lipid metabolism [127].

The role of eicosanoids in sunburn is multifaceted. PGE₂ can mediate the initial inflammatory phase but later on it can play a part in the resolution of inflammation and tissue repair [128]; furthermore, continuous production of PGE₂ in unresolved inflammation may contribute to the immune suppression observed in photocarcinogenesis [120]. 12-HETE is a potent leukocyte chemoattract but can also be involved in keratinocyte and fibroblast mediated healing events [31, 35], whilst 15-HETE and 13-HODE may assist in restricting pro-inflammatory signals [65, 83].

4. Effect of PUFA and antioxidants in cutaneous inflammation

The active involvement of fatty acids in skin health and epidermal barrier function justifies the choice of systemic supplementation with n-3PUFA as an effective strategy for the improvement of inflammatory conditions [129]. Long chain n-3PUFA effect eicosanoid production through their ability to offer alternative substrates to lipid metabolizing enzymes and through their role in cell signalling, gene expression and, consequently, enzyme protein levels [130]. Generally, COX-mediators of n-3PUFA, such the EPA product PGE₃, are considered less inflammatory and 12-LOX products, such 12-HEPE, less potent chemoattractants than their AA-counterparts. However, it is also possible that the formation

of these mediators reduces the effective concentration of AA-eicosanoids resulting in a less inflammatory environment. Furthermore, EPA inhibits COX-2 expression in many cell types, although there is some evidence that this may not be the case in human keratinocytes [131] suggesting the need to further elucidate the response of epidermal and dermal cells.

Human skin responds to nutritional intervention and studies with fish oil n-3PUFA have shown reduced erythema and decreased levels of PGE₂ following UVR treatment [132]. This finding points towards a possible chemopreventive strategy to address the harmful effects of solar radiation. The role of n-3PUFA-derived mediators has also been considered in wound healing where the profile of lipid chemoattractants can influence the leukocytic infiltrate and degree of epithelization [133-135]. Finally, as discussed, dietary interventions with n-3PUFA have shown amelioration in psoriasis and atopic dermatitis, strengthening the evidence for the beneficial role of n-3PUFA in cutaneous health [106, 118].

Finally, the role of oxidative stress in many aspects of cutaneous biology has raised interest in systemic or topical use of antioxidants as potential modulators of skin health, with a number of natural products being assessed for their ability to exert such protective effects. Plant polyphenols exhibit potent antioxidant properties and, when tested in animal models or cells in vitro, have shown potent beneficial effects related to inflammation, photoprotection, immunomodulation [136, 137]. Green tea and cocoa bean catechins are very promising bioactives for skin health with aspects of their bioactivities are mediated through interactions with cutaneous eicosanoids as shown by reports on the reduction of UVR-induced erythema and COX-2 activity in mice, reduction of COX-2, EP2 and EP4 expression, and inhibition of COX and LOX-products [138, 139]. However, placebo-controlled clinical studies are needed in order to evaluate their effect in skin inflammation and substantiate any relevant claims.

5. Concluding remarks

Skin is not only the biggest organ of the body but it is immediately visible so that any health issues affecting its appearance raise concern. Inflammation can be part of physiological self-regulated responses or underpin the pathology of cutaneous diseases; therefore a detailed understanding of the mediators involved in each case can be valuable in directing the effort for new therapeutics. Lipidomic approaches, supported by recent developments in lipid analysis, have not only made possible the identification of novel bioactive lipids, but have offered detailed insight to the complexity of mediators involved in the various phases of inflammation. For example, when applied to sunburn skin, lipidomics showed the contribution of more lipid species than previously thought, and has raised questions about their role [22]. Nutritional supplementation with PUFA alters the pool of fatty acids available for eicosanoid biosynthesis, manipulates the profile of known mediators and permits formation of new species, such as EPA and DHA-derived resolvins and protectins [4]. The identification of such lipids in human skin is of great interest since it can explain the beneficial effect of systemic or topical application of PUFA. Furthermore, nutrigenomics applied in tandem with lipidomics and proteomics, during controlled clinical investigations, are needed to elucidate the exact role of various anti-inflammatory bioactives showing beneficial cutaneous effects.

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Table 1: Biological effects of selective eicosanoids involved in cutaneous inflammation

Metabolite	Biological Effect	Cellular Origin
PGE ₂	vasodilatation; immunosuppression; chemotaxis; proliferation; pigmentation	epidermal keratinocytes; dermal fibroblasts
PGD ₂	Immunomodulation	Langerhans cells; mast cells; epidermal keratinocytes
12S-HETE	chemotaxis - leukocyte migration; proliferation	epidermal keratinocytes; Langerhans cells; dermal fibroblasts
15S-HETE	anti-inflammatory; counteracts 12S-HETE and LTB ₄ effects	epidermal keratinocytes; dermal fibroblasts
13S-HODE	anti-inflammatory; anti-proliferatory	epidermal keratinocytes; dermal fibroblasts
15S-HETrE	anti-inflammatory	epidermal keratinocytes; dermal fibroblasts
LTB ₄	Chemotaxis	Infiltrating leukocytes; epidermal keratinocytes (low levels)

Figure legends

Figure 1: Schematic overview of biosynthetic pathways for the main biologically relevant oxygenated products of polyunsaturated fatty acids. acCOX: acetylated COX; AT-RvD₁: aspirin triggered RvD₁.

