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Fatty acids and related lipid mediators in the regulation of cutaneous inflammation

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ABSTRACT

Human skin has a distinct profile of fatty acids and related bioactive lipid mediators that regulate many aspects of epidermal and dermal homeostasis, including immune and inflammatory reactions. Sebum lipids act as effective antimicrobial agents, shape immune cell communications and contribute to the epidermal lipidome. The essential fatty acid linoleic acid is crucial for the structure of the epidermal barrier, while polyunsaturated fatty acids act as precursors to eicosanoids, octadecanoids and docosanoids through cyclooxygenase, lipoxygenase and cytochrome P450 monooxygenase-mediated reactions, and endocannabinoids and N-acyl ethanolamines. Cross-communication between these families of bioactive lipids suggests that their cutaneous activities should be considered as part of a wider metabolic network that can be targeted to maintain skin health, control inflammation and improve skin pathologies.

ABBREVIATIONS

2-AG: 2-arachidonoyl glycerol; AA: Arachidonic acid; AEA: Arachidonoyl ethanolamine; CB: Cannabinoid receptor; COX: Cyclooxygenase; CYP: Cytochrome P450; DHA: Docosahexaenoic acid; DHET: Dihydroxyeicosatrienoic acid; EET: Epoxyeicosatetraenoic acid; EGF: Epidermal growth factor; EPA: Eicosapentaenoic acid; EPEA: Eicosapentaenoyl ethanolamine; HDHA: Hydroxydocosahexaenoic acid; HEPE: Hydroxyeicosapentaenoic acid; HETE: Hydroxyeicosatetraenoic acid; HODE: Hydroxyoctadecadienoic acid; IL: Interleukin; LA: Linoleic acid; LOX: Lipoxygenase; LPS: Lipopolysaccharide; LT: Leukotriene; MUFA: Monounsaturated fatty acid; NAE: N-acyl ethanolamine; OA: Oleic acid; OEA: Oleoyl ethanolamine; PA: Palmitic acid; PEA: Palmitoyl ethanolamine; PG: Prostaglandin; PUFA: Polyunsaturated fatty acid; SFA: Saturated fatty acid; SPM: specialised pro-resolving mediator; UVR: Ultraviolet radiation.

1. INTRODUCTION

Fatty acids have long been recognised for their importance in skin health, and essential fatty acid deficiencies result in fatal epidermal barrier failure, characterised by desquamation and skin lesions (1, 2). Altering the cutaneous fatty acid profile through diet or nutritional supplementation has been reported to ameliorate inflammatory conditions [reviewed in (3-6)]. As well as having direct effects on signalling pathways, gene transcription, inflammatory and immune responses, many of the fatty acid-mediated bioactivities are attributed, at least in part, to the formation of bioactive derivatives. These lipid mediators are produced via sequential enzymatic reactions that typically start with the liberation of the relevant fatty acid precursor from membrane phospholipids, following the action of inflammatory or other stimuli that activate the relevant phospholipases (7-9). Once cleaved from the cellular membranes, free fatty acids can be converted into an array of bioactive mediators following the action of prostaglandin-endoperoxide synthases (cyclooxygenases; COX), lipoxygenases (LOX) and cytochrome P450 monooxygenases (CYP), as well as transcellular and non-enzymatic reactions. **Figure 1** shows a diagrammatic outline of the main biochemical reactions mediating the biotransformation of the key polyunsaturated fatty acid (PUFA) arachidonic acid (AA; C20:4n-6). The metabolism of various cutaneous PUFA occurs in a similar way, and results in an array of eicosanoids, docosanoids, octadecanoids, endocannabinoids and N-acyl ethanolamines (NAE), that have all been implicated in numerous aspects of cutaneous inflammation (3, 5). This review article aims to give an overview of the most important fatty acids that are found in human skin, discuss their properties, and introduce the biochemical pathways leading to the formation of bioactive lipid mediators involved in skin cell biology. A detailed appreciation of the profiles and balance of cutaneous fatty acids and related metabolites is important as this system can be targeted to maintain skin health, regulate inflammation, and improve skin pathologies.

2. CUTANEOUS FATTY ACIDS

2.1. SEBUM FATTY ACIDS

Human sebum has a unique fatty acid profile that contains the sebum-characteristic sapienic acid (C16:1n-10), as well as palmitic acid (PA; C16:0), palmitoleic acid (C16:1n-7), and oleic acid (OA; C18:1n-9) (10-12). Importantly, sebum-derived fatty acids have been shown to be effective antimicrobial agents for bacteria such as *Porphyromonas gingivalis*, *Staphylococcus aureus* and *Staphylococcus epidermidis*, and play an active role in shaping the cutaneous microbiome (11-16). They are also actively involved in epidermal homeostasis and immune cell communications. It has been shown that OA can alter intracellular calcium in normal human keratinocytes and murine skin, leading to hyperproliferation and increased trans-epidermal water loss, while palmitoleic acid can cause keratinocyte hyperplasia in mouse skin (17, 18). Overall, sebum fatty acids contribute significantly to skin health and epidermal defence functions (16, 19), directly affecting epidermal keratinocytes, informing the cutaneous immune barrier, and protecting the surface of the skin from pathogenic microorganisms.

2.2. FATTY ACIDS IN EPIDERMIS AND DERMIS

Cutaneous fatty acids found in the epidermis and dermis are key determinants of skin health. The epidermis is the outermost skin layer and comprises a basal layer of proliferating keratinocytes, which switch to differentiate and migrate upwards to form multiple stratified layers of denucleated cells at the surface (19). The most abundant fatty acids in this layer are saturated fatty acids (SFA) i.e. PA and stearic acid, and monounsaturated fatty acids (MUFA) such as OA (~23% each) (20). The dermis contains high levels of unsaturated fatty acids, mostly OA (~45%), as well as the SFA PA (~20%) (20). The ratio between SFA and MUFA represents the activity of $\Delta 9$ desaturase, an enzyme important for skin health: inhibition of $\Delta 9$ desaturase was shown to reduce proliferation of dermal fibroblasts and disturb the cellular response to growth factors, whilst deletion of the $\Delta 9$ desaturase gene in

an animal model resulted in a ulcerative dermatitis, dry, flaky skin and severe alopecia (21-23).

Polyunsaturated fatty acids (PUFA) are found at lower levels than SFA or MUFA, e.g. linoleic acid (LA; C18:2n-6) and AA comprise approximately 9-10 % and 2-3 % of the epidermal fatty acids, respectively. However, PUFA are very important for skin health [reviewed in (20)]. Linoleic acid is an essential fatty acid, an integral component of acylceramides, and insufficient levels result in impaired formation of the epidermal permeability barrier (24, 25). Indeed, genetic abnormalities in elongase enzymes (for example ELOV4 deficiency), render the skin unable to produce long chain fatty acids, and the barrier fails due to an absence of acylceramides (26). Additionally, the epidermis relies on the dermis and systemic supplementation to provide long chain PUFA such as AA, eicosapentaenoic acid (EPA; C20:5n-3) and docosahexaenoic acid (DHA; C22:6n-3), as it lacks the necessary $\Delta 5$ and $\Delta 6$ desaturases to form these long chain PUFA from C18 fatty acid precursors (27). Thus the cutaneous profile of these fatty acids is greatly influenced by diet, and responds to nutritional supplementation (4, 5, 28). Animal and clinical studies, as well as work with preclinical models, have shown that PUFA supplementation can confer photoprotection, improve wound healing and reduce inflammatory markers (4, 29, 30). Although the detailed molecular mechanisms of how fatty acids influence skin health are not always understood, often their effects can be attributed to formation of bioactive metabolites, as discussed below.

3. FATTY ACID-DERIVED LIPID MEDIATORS

3.1. PROSTANOIDS

The family of prostanoids includes various prostaglandins (PG), thromboxanes (TX) and prostacyclin (PGI₂), all formed from 20-carbon PUFA precursors (i.e. AA, dihomo-gamma linolenic acid (DGLA; C18:3n-6) and EPA), through the activities of constitutive COX-1 and/or inducible COX-2, and terminal prostanoid synthases (**Figure 1**). The bioactivities of

prostanoids are mediated through a series of G protein coupled receptors that have been identified in many cell types, including skin cells [reviewed in (3, 5, 7)].

Keratinocytes and fibroblasts, as well as skin-resident immune cells, produce a number of prostanoids including PGE₂, PGE₁, PGE₃, PGD₂, PGF_{2α}, PGI₂, and TXB₂ (31-33). One of the best studied species is PGE₂, which regulates keratinocyte and fibroblast growth and proliferation through production of growth factors and cytokines, including fibroblast growth factor, epidermal growth factor (EGF), tumour necrosis factor-α, interleukin (IL) -1, IL-6 and IL-8 (34-39). PGE₂ also acts as a potent immunomodulatory stimulus, triggering recruitment of T lymphocytes and maturation of dendritic cells, both important for skin immunity (40-42). These changes are associated with vasodilation and further recruitment of immune cells, as demonstrated by the increased accumulation of neutrophils and oedema in rodent skin following a local injection of PGE₁ and PGE₂ (43, 44). Conversely, PGE₃ was not mitogenic in murine epidermal cultures or a dermal fibroblast cell line, and it has been suggested to play an anti-inflammatory role (45-47).

PGD₂ can also stimulate T-cell and eosinophil migration (48). In skin, it is produced mainly by Langerhans cells and dermal mast cells, and high levels of PGD₂ have been linked to hair loss and androgenetic alopecia (49). The inhibition of hair growth involves a potent apoptotic action of PGD₂ on follicular keratinocytes, although it has also been shown that PGD₂ may also act as an anti-inflammatory mediator, depending on the cell type and time of its production (50).

Multiple studies have shown increased production of cutaneous prostanoids following the upregulation of COX-2 in response to inflammatory stimuli, as observed in the sunburn reaction and wound healing (33, 51, 52). Interestingly, COX-2 inhibitors were found to cause a significant delay to wound healing, with wounds showing significant reduction in PGE₂ levels, epidermal proliferation, angiogenesis and extracellular matrix (53, 54). However, mice showed accelerated wound healing when catabolism of PGE₂ was inhibited (55, 56). This

finding highlights the role of skin prostaglandins in regulating the early phases of inflammation, which are crucial for efficient resolution and tissue remodelling. Non-steroidal anti-inflammatory drugs inhibit COX-1 and -2 activity, and therefore prostanoid production, which may reduce skin inflammation. However free fatty acids are then metabolised through other enzyme pathways. Indeed, when cutaneous COX-derived prostaglandin production was blocked by indomethacin, LOX metabolism dominated and an increase in 12-hydroxyeicosatetraenoic acid (HETE) was observed, so although erythema was reduced, there was a greater inflammatory infiltrate in the skin (57). Interestingly, PGE₂ has recently been shown to mediate a phase of post-inflammatory immune-suppression, believed to be important for prevention of an autoimmune response, highlighting its importance past the initial inflammatory phase (58).

3.2. HYDROXY FATTY ACIDS

Lipoxygenases (LOX) produce a series of hydroxy fatty acids and leukotrienes (LT) (59, 60). Human and animal skin express a number of LOX isoforms, e.g. 5-, 8-, 12- and 15-LOX, that can utilise a range of fatty acid substrates, including AA, LA, EPA, DGLA and DHA [reviewed in (3, 5, 7)] (**Figure 1**). The 12*R*-LOX is unique to mammalian skin cells and has been purported to be involved in cutaneous inflammation, given observations of 12*R*-HETE in psoriasis skin. Its main role, however, is believed to be linked to the formation of the epidermal lipid barrier, in conjunction with the epidermis-type eLOX-3. These two enzymes perform consecutive oxidisations of the linoleic acid in acylceramides, enabling its linkage to cornified envelope proteins, which is crucial for an effective epidermal barrier (60-63). Indeed, congenital ichthyosis has been linked to mutations in 12*R* LOX and eLOX-3 (64, 65). LOX reactions are also involved in the transcellular metabolism of PUFA to generate lipoxins from AA, resolvins and protectins from EPA and DHA, and maresins from DHA, collectively known as specialised pro-resolving mediators (SPMs) for their anti-inflammatory functions (66). Although a number of their hydroxy fatty acid precursors have been found in skin, before and after PUFA supplementation, the SPMs themselves have not been identified in

skin to-date, and their importance in cutaneous health and disease remains unclear (29, 67, 68).

Linoleic acid-derived hydroxyoctadecadienoic acids (HODE) are the most abundant hydroxy fatty acids found in human skin (20). Both 9- and 13-HODE are potent chemotactic agents, and cause increased infiltration and migration of neutrophils and macrophages, as well as regulating the proliferation and differentiation of epidermal keratinocytes (69-72). Recently, HODE have been considered as important mediators in inflammatory pain, although evidence for their role in cutaneous pain is limited (73, 74).

Leukotrienes (LT) are 5-LOX derivatives of AA with potent chemotactic properties, and induce neutrophil infiltration in inflamed skin. However, the cutaneous activity of 5-LOX is relatively low, and increased formation of LT has been attributed to infiltrating immune cells and not resident skin cells (75, 76). 12-HETE and 15-HETE are the main LOX-derived products of AA in skin (20). 12-HETE is considered pro-inflammatory, and has been associated with increased infiltration of leukocytes (57, 77, 78). 15-HETE has been shown to decrease levels of LTB₄ and 12-HETE, and stimulate the remodelling of injury sites and production of EGF in endothelial cells, a property important in the later stages of inflammation (79-82). Both 12-LOX and 15-LOX protein expression has been found upregulated in human skin following exposure to UVR, with concomitant increases in 12- and 15-HETE (33), while increased 15-LOX gene expression in the human skin has been associated with a reduction of pro-inflammatory IL-6 and TNF α , epidermal thickness and epidermal cell migration (83). Interestingly, a study on mice lacking the 12/15LOX gene showed a reduced number of mesenchymal stem cells with disturbed kinetics in the wounded dermis, which has implications for tissue remodelling (84). Additionally, the 12-LOX DHA product, 14-HDHA improved all stages of the wound healing process in mice, via enhanced reepithelization, granulation and angiogenesis (85). Hence, these findings confirm a strong involvement of LOX-derived PUFA mediators in sustaining the later stages of inflammation, when COX-mediated production of prostaglandins has decreased (33).

3.3. EPOXY FATTY ACIDS

The cytochrome P450 (CYP) isozymes CYP2C and CYP2J are epoxygenases that mediate the production of epoxyeicosatrienoic acids (EET) from AA (**Figure 1**). These epoxides are rapidly transformed by the soluble epoxide hydrolase (sEH) to dihydroeicosatetraenoic acids (DHET) that exhibit much reduced bioactivities. Furthermore, CYP-mediated oxidations can produce a range of HETE similar to the ones formed by LOX. Other PUFA substrates for CYP reactions include LA, EPA and DHA (86-88).

While the role of DHET in skin inflammation is unclear, cutaneous functions of EET are emerging. Increasing endogenous levels of EET via inhibition of sEH improved vascularization in an engineered skin substitute (89). Additionally, topical application of EET accelerated epithelialization in the hairless mouse, while CYP inhibitors significantly delayed wound closure (90, 91). Analysis of individual EET has revealed that 11,12 EET increases angiogenesis and improves wound healing in diabetic mice, while 14,15 EET is directly involved in epidermal barrier function through regulation of involucrin and promotion of the cornification of human and murine keratinocytes (92, 93). The non-epoxy CYP product 20-HETE appears to have a role in angiogenesis, as it leads to increased proliferation and migration of endothelial cells (94, 95). Despite a limited understanding of the role of CYP reactions and resulting epoxy fatty acids in skin health, these compounds appear to be important during later stages of inflammation and wound healing, and further research to elucidate EET and DHET function in skin is required (96-98).

3.4. ENDOCANNABINOIDS AND N-ACYL ETHANOLAMINES

Human skin produces the classic endocannabinoids arachidonoyl ethanolamine (anandamide; AEA) and 2-arachidonoyl glycerol (2-AG)), as well as a range of N-acyl ethanolamines (NAE) (20) (**Figure 1**). AEA and 2-AG are known ligands for the cannabinoid receptors CB1 and CB2, the expression of which has been reported in the epidermis, dermo-epidermal junction and dermis (20, 99). AEA and 2-AG derive from phospholipid-esterified

arachidonic acid, and can be further metabolised by COX, LOX and CYP enzymes, however the prevalence of these species in human skin has not been confirmed (9). Many of the fatty acid-derived NAE present very low or no affinity to CB1 or CB2, and are believed to act through other receptors such as vanilloid receptor 1 (TRPV1) and PPAR α (100, 101).

Endocannabinoids and NAE are involved in various cutaneous functions, including keratinocyte differentiation (102, 103). AEA inhibits the proliferation of human epidermal keratinocytes and dermal fibroblasts via induction of apoptosis (103, 104). This apoptotic function of AEA was also observed in human sebocytes, where both AEA and 2-AG stimulated differentiation, maturation and lipogenesis via CB2-mediated signalling (105, 106). Furthermore, AEA limits excessive mast cell activation in hair follicles, highlighting its function in the regulation of dermal inflammation (107). Palmitoyl ethanolamine (PEA) and oleoyl ethanolamine (OEA) have anti-inflammatory and analgesic effects, and PEA has been shown to reduce itching in a murine allergic dermatitis model, while linoleoyl ethanolamine (LEA) reduced lipopolysaccharide (LPS)-induced inflammation in macrophages, thereby improving contact dermatitis (108-111). The n-3 PUFA-derived eicosapentaenoyl ethanolamine (EPEA) and docosahexaenoyl ethanolamine (DHEA) have been shown to mediate anti-inflammatory protective mechanisms and reduction of itching and pain, suggesting a potentially important role in skin (112-114).

Endocannabinoids and NAEs may also serve as immunomodulatory mediators in the skin, and have been found to be upregulated during various types of skin inflammation (99, 115). AEA and 2-AG levels were increased after UVR treatment of HaCaT keratinocytes (116), while in study involving different keratinocyte and fibroblast cell lines, AEA, 2-AG and CB1 and CB2 expression were found to decrease following UVR irradiation (117, 118). A clinical study (119) reported increased 2-AG but stable levels of AEA, OEA and PEA in the serum of human volunteers subjected to a repetitive cutaneous exposure to simulated solar UVR (119). Similarly, the skin of human volunteers irradiated with low-dose UVR did not show any

changes in levels of endocannabinoids and NAE species, although there was an increase of stearoyl ethanolamine, LEA, OEA and PEA following sodium lauryl sulfate application (120) . Mustard vesicants also increased levels of AEA and 2-AG, and increased expression of CB receptors, in murine skin *in vivo*, although only several days after stimulation (121).

Overall, it is believed that endocannabinoids and NAE may act to quench inflammation, and their production may prevent an excessive inflammatory response in the skin. Upregulation of CB1/CB2 receptor expression was observed in fibroblasts and macrophage-like cells during wound healing in rats (104), while 2-AG and CB1 activation are associated with reduced immune infiltration, scarring and accelerated wound closure in epithelial cells. However, CB1 activation in the dermis slowed wound healing, suggesting different roles for endocannabinoids in the different skin compartments (104, 122).

4. CONCLUSION

Fatty acids are crucial for skin health, as they contribute to the structural and functional integrity of the epidermis. Additionally, their metabolism into a range of bioactive mediators that regulate various aspects of epidermal and dermal homeostasis, including immune and inflammatory reactions, shows their importance for cutaneous health and disease. The availability of precursor fatty acids, coupled to the expression and activity of lipid metabolising enzymes, determines the profile of cutaneous lipid mediators. COX-derived prostaglandins and LOX-derived hydroxy fatty acids respond to most inflammatory stimuli; the properties of these mediators are continually being elucidated. CYP-derived lipid mediators have not been extensively studied in the skin, but there is evidence supporting their involvement in tissue remodelling. Finally, endocannabinoids and NAEs appear to support homeostasis and transcellular signalling during cutaneous inflammation, and may prevent excessive immune responses. The cross-communication between these families of fatty acid-derived lipids suggests that their properties should not be studied in isolation, and

their prevalence should be considered as part of a wider metabolic network that regulates cutaneous reactions.

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Table 1: Examples of lipids and some of their roles in skin

Lipid	Biological role
Sapienic acid	Antimicrobial (13, 14)
Oleic acid	Promotes keratinocyte proliferation (17)
Palmitoleic acid	Promotes keratinocyte proliferation (18)
Linoleic acid	Essential component of epidermal acylceramides (24)
PGE ₂	Regulates fibroblast and keratinocyte growth (34, 36, 37); recruitment of immune cells (40, 41); vasodilation (43); wound healing (54-56); post-inflammatory immune suppression (58)
PGE ₁	Recruitment of immune cells (43)
PGD ₂	Stimulates immune cell migration (48); hair loss (49)
9-HODE	Immune cell recruitment; pain (74)
13-HODE	Immune cell recruitment; pain (74)
LTB ₄	Immune cell recruitment (76)
12-HETE	Immune cell recruitment (57)
15-HETE	Suppresses inflammatory cytokine and lipid mediator production (79, 81, 83); vascular remodelling (82)
14-HDHA	Reepithelialisation (85); granulation (85); angiogenesis (85)
EETs	Vascularisation (89); epithelialisation (90, 91); angiogenesis (92); keratinocyte cornification (93)
AEA	Inhibits fibroblast and keratinocyte proliferation (103, 104); suppresses mast cell activation (107)
PEA	Reduces itch (108); analgesic (108)
OEA	Analgesic (109)
LEA	Suppresses macrophage activation (111)
EPEA	Reduces itch (112); analgesic (113)
DHEA	Reduces itch (112); analgesic (113)

FIGURE LEGEND

Figure 1. Schematic outline of the main enzymatic reactions involved in the arachidonic acid cascade, showing the conversion of this polyunsaturated fatty acid to various classes of bioactive lipid mediators potentially important in cutaneous biology. Although the relevant enzymes are expressed in skin cells, not all mediators have been identified in human skin to date. AEA: arachidonoyl ethanolamine; COX: cyclooxygenase; CYP450: cytochrome P450; EET: epoxyeicosatrienoic acid; FAAH: fatty acid amide hydrolase; HETE: hydroxyeicosatetraenoic acid; 12-HETE-EA: 12-hydroxyeicosatetraenoic acid ethanolamine; LOX: lipoxygenase; LXA₄: lipoxin A₄; NAPE-PLD: N-acyl phosphatidylethanolamine phospholipase D; NArPE: N-arachidonoyl phosphatidylethanolamine; PC: phosphatidylcholine; PGE₂: prostaglandin E₂; PGE₂-EA: prostaglandin E₂ ethanolamine (prostamide); PLA₂: phospholipase A₂.