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Current knowledge of the implication of lipid mediators in psoriasis

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The skin is an organ involved in several biological processes essential to the proper functioning of the organism. One of these essential biological functions of the skin is its barrier function, mediated notably by the lipids of the stratum corneum, and which prevents both penetration from external aggression, and transepidermal water loss. Bioactive lipid mediators derived from polyunsaturated fatty acids (PUFAs) constitute a complex bioactive lipid network greatly involved in skin homeostasis. Bioactive lipid mediators derived from n-3 and n-6 PUFAs have well-documented anti- and pro-inflammatory properties and are recognized as playing numerous and complex roles in the behavior of diverse skin diseases, including psoriasis. Psoriasis is an inflammatory autoimmune disease with many comorbidities and is associated with enhanced levels of pro-inflammatory lipid mediators. Studies have shown that a high intake of n-3 PUFAs can influence the development and progression of psoriasis, mainly by reducing the severity and frequency of psoriatic plaques. Herein, we provide an overview of the differential effects of n-3 and n-6 PUFA lipid mediators, including prostanoids, hydroxy-fatty acids, leukotrienes, specialized pro-resolving mediators, N-acylethanolamines, monoacylglycerols and endocannabinoids. This review summarizes current findings on lipid mediators playing a role in the skin and their potential as therapeutic targets for psoriatic patients.

KEYWORDS

psoriasis, lipid mediator, skin, polyunsaturated fatty acids, inflammation

Introduction

Lipid metabolism is currently a major research interest as lipids play crucial roles in all biological mechanisms, including the formation and functioning of the skin barrier. Interest in the metabolism of n-3 and n-6 polyunsaturated fatty acids (PUFAs) was first shown by Burr and Burr in the 1920s, in studies investigating the effects of different

PUFAs on rodent health through diet supplementation (1). These studies led to the identification of two polyunsaturated fatty acids, linoleic acid (LA, n-6 PUFA) and α -linolenic acid (ALA, n-3 PUFA), which cannot be synthesized by mammalian organism and whose presence in the body is therefore dependent on food intakes. It was later shown that PUFAs and PUFA-derived bioactive lipid mediators play important roles in the regulation of biological processes by mediating inflammatory responses. Bioactive lipid mediators can be found throughout the body, and each tissue has a characteristic bioactive lipid mediator profile. This specificity depends on the expression, activity, and affinity of different PUFAs, and of the proteins involved in the biosynthesis of bioactive lipid mediators, which vary among tissues (2). Moreover, the bioactive lipid mediator profile of an individual is largely affected by their nutritional status (3, 4).

Studies on the Inuit paradox in the 1970s highlighted the diverse benefits of high n-3 PUFA consumption on the risk of developing cardiovascular diseases (5). Since then, many clinical studies have investigated the effects of diet supplementation with n-3 PUFAs on the risk of developing cancer, atherosclerosis and inflammatory skin diseases, such as psoriasis (6–8). In parallel, many bioactive lipid mediators derived from n-6 PUFAs were being discovered and associated with leukocyte chemoattractant and pro-inflammatory functions (9, 10). Following these studies, n-3 and n-6 PUFA-derived bioactive lipid mediators were recognized for their unique and complementary inflammatory properties (11). Those derived from n-3 PUFAs were primarily known for their anti-inflammatory, beneficial, and protective properties, in contrast to those derived from n-6 PUFAs, which are better known for their pro-inflammatory properties. The n-3 and n-6 PUFAs are metabolized by the same enzymes; consequently, their transformation is regulated by substrate competition (12). The duality of the effects of the two PUFA families led to a concept widely discussed in the literature, namely the balance between n-3 and n-6 PUFAs (13, 14). However, the effects of PUFAs were shown to be much more extensive and complex. For instance, both n-3 and n-6 PUFA-derived bioactive lipid mediators can have pro- or anti-inflammatory effects, leading to contradictory conclusions. Indeed, n-3 and n-6 PUFAs follow multiple complex metabolic pathways, making it difficult to establish their precise mode of action (15). At the beginning of the 21st century, a new concept emerged, reporting that the acute inflammatory reaction progresses in two phases: the initiation and the resolution of inflammation (16). Numerous studies appear to convincingly show that lipid mediators are produced in a sequential and organized manner to regulate the inflammatory response (17–21). Lipid mediators derived from n-6 PUFAs, such as prostaglandin E₂ (PGE₂) and leukotriene B₄ (LTB₄), would be produced during the initiation phase in order to promote in particular the recruitment and the adhesion of

immune cells, as well as the dilation of blood vessels (22). The resolution phase would be mediated by the production of lipid mediators derived from n-3 PUFAs and more specifically by specialized pro-resolving mediators (SPMs) (23, 24).

Psoriasis is an inflammatory skin disease in which a dysregulation in lipid mediators derived from n-6 PUFAs has been reported (25, 26). Hence, n-3 PUFAs have been investigated as potential treatment options in various studies. While the results of these studies are varied, the evidence seems to favor a beneficial effect of n-3 PUFAs on psoriasis. This manuscript reviews current knowledge of the implication of n-3 and n-6 PUFAs, as well as their related lipid mediators, in psoriasis and their potential therapeutic effects on this skin condition.

Skin physiology

The skin is a crucial organ that is essential to human survival. Among its multiple roles, the barrier function is undeniably important: the skin barrier prevents the bodily penetration of external substances while maintaining the hydration of the body by preventing water loss (27). The structure of the skin is divided into three layers: hypodermis, dermis, and epidermis. The hypodermis is the deepest layer, mainly constituted of adipocytes playing an important role in thermoregulation and maintaining the energy reserve of the body. The dermis, the middle layer, is a connective tissue composed of fibroblasts surrounded by a rich extracellular matrix conferring suppleness and elasticity to the skin (28). It contains blood vessels, nerves, and skin appendages including sweat glands and hair follicles. This layer supports and nourishes the epidermal cells by diffusion (28, 29). The epidermis is the skin's most superficial layer, a squamous epithelium mainly constituted of keratinocytes and in which other cell types are incorporated including Langerhans cells, Merkel cells, and melanocytes (28). Skin immunity is crucial for protecting the body from harmful external aggressions. The immune system of the skin involves both innate and adaptive immunity. The innate immunity includes two lines of defense, one provided by epithelial tissues and the other provided by specific immune cells, including neutrophils, monocytes, macrophages, and natural killer cells (30). In fact, keratinocytes, along with neutrophils, modulate the immune status of the skin by producing large quantities of antimicrobial peptides (AMPs), including psoriasin (S100A7), calgranulin A (S100A8), B (S100A9), β -defensins and cathelicidin (CAMP) (31, 32). Subsequently, under the influence of inflammatory stimuli, cytotoxic T cells (CD8+), which eliminate infected and cancerous cells, and helper T (Th) cells (CD4+), which coordinate humoral immunity and stimulate B cells, can infiltrate the skin (33). The dermis permanently harbors immune cells, including dendritic cells and memory T cells (34).

The constant renewal of the epidermis includes the proliferation, differentiation, and elimination of keratinocytes by desquamation, with a cycle lasting approximately 28 days. The morphological, structural, and protein changes observed during this process permit the division of the epidermis into four layers, namely the stratum basal, stratum spinosum, stratum granulosum, and stratum corneum (35). The keratinocytes of the stratum basal proliferate to ensure the renewal of the epidermis (28). As the cells proliferate, they migrate towards the stratum spinosum, where the differentiation of the keratinocytes is induced through the action of desmosomes linking the cells together. The differentiation of epidermal keratinocytes is a complex but perfectly orchestrated process, leading to cell death and the formation of a semi-permeable barrier: the stratum corneum (35, 36). This process causes drastic changes such as the complete flattening of the cells and the degradation of their organelles and nuclei, ending in the formation of corneocytes (35). The stratum corneum is organized in a brick-and-mortar pattern, with the bricks being the corneocytes and the mortar the lipid matrix between the cells, thus providing a tight structure. The lipid matrix alone corresponds to 10% of the weight of the stratum corneum, and is composed of 45% ceramides, 30% cholesterol, and 15% free fatty acids (37). The cells of the stratum corneum eventually desquamate (38).

The epidermis has an important lipid metabolism, which is modulated during epidermal differentiation to ensure the production of the stratum corneum lipid matrix (39). The basal layer of the epidermis has a high rate of phospholipid biosynthesis due to the cell division process, which requires the formation of new cell membranes (40). Phospholipids account for 45% of lipids in the basal and spinous layers, 25% in the stratum granulosum, and less than 5% in the stratum corneum (28). In the spinous layer, fatty acids from cell membrane phospholipids are hydrolyzed and transported to the endoplasmic reticulum (41). They are then used for the synthesis of more complex lipids, including ceramides and triglycerides (39). Cholesterol is also synthesized *de novo* in this layer (42). Newly formed lipids are subsequently stored in vesicles produced by the Golgi apparatus, called lamellar bodies. Lamellar bodies are 0.3 μm ovoid secretory organelles, containing mostly lipids (phospholipids, cholesterol, glucosylceramides, and sphingomyelins) and several proteins (43). These proteins consist mainly of glucosidase, sphingomyelinase, secretory phospholipase A2 (sPLA2) as well as several neutral and acidic lipases, kallikreins 7 and 8, cathepsin D, inhibitory proteases, caveolin-1, and corneodesmosins (43). During cell differentiation, there is an accumulation of lamellar bodies in keratinocytes up to the granular layer where they are finally extruded, releasing their lipid contents between stratum corneum cells (39). Following their secretion, lipids are subsequently metabolized by co-secreted proteins (Figure 1) (43). Phospholipids are hydrolyzed

by phospholipase A₂ (PLA₂) to generate free fatty acids for the stratum corneum lipid matrix as well as glycerol. This glycerol is responsible for the hydration of the stratum corneum (43). The elongation of fatty acids by elongases (ELOVL) is a crucial step in epidermal differentiation, since it allows the generation of free fatty acids with very long chains, which are characteristic of the stratum corneum (44, 45). Additionally, a group of ω -hydroxy-ceramides containing a LA moiety, the acylceramides, are particularly important in the proper organization of the lipid matrix. Since they are covalently bound to the proteins of the cornified envelope, they serve as a scaffold for the other lipids, which allows an optimal bilamellar organization of the lipid matrix (46). Eventually, cholesterol sulfate is converted to cholesterol which allows the desquamation of corneocytes (43).

n-3 and n-6 PUFA metabolism

PUFAs can be classified into two major families according to the position of the last double bond with respect to the methyl terminus of the acyl chain, being either n-3 or n-6 PUFAs. Both follow parallel metabolic pathways involving the same enzymes (Figure 2). Alpha-linolenic acid (ALA, 18:3n-3) and linoleic acid (LA, 18:2n-6) are metabolized to stearidonic acid (SDA, 18:4n-3) and gamma-linolenic acid (GLA, 18:3n-6), respectively, by the delta-6-desaturase (D6D). This represents the slowest step in the metabolic pathway, and therefore D6D activity partly regulates the PUFA biosynthetic pathway (47). Interestingly, D6D has a higher affinity for LA than for ALA (48). Moreover, the human epidermis has a low delta-5-desaturase (D5D) and D6D activity, which makes the production of long-chain n-3 PUFAs dependent on food intake (49). Both products then undergo an elongation cycle to produce eicosatetraenoic acid (ETA, 20:4n-3) and dihomo-gamma-linolenic acid (DGLA, 20:3n-6), respectively, followed by desaturation by D5D to form eicosapentaenoic acid (EPA, 20:5n-3) and arachidonic acid (AA, 20:4n-6). These metabolites are subsequently transformed into n-3 docosapentaenoic acid (n-3 DPA, 22:5n-3) and docosatetraenoic acid (DTA, 22:4n-6), and into docosahexaenoic acid (DHA, 22:6n-3) and n-6 DPA (22:5n-6). This last reaction is a β -oxidation requiring the transfer of precursors from the endoplasmic reticulum to the peroxisomes (47). Retro-conversion mechanisms can also occur, as DHA can be converted to EPA. However, these reactions are not very efficient (48). N-3 and n-6 PUFAs have structural and metabolic roles in the body: they serve as energy sources, are major constituents of cell membranes, are involved in gene regulation and have roles in cellular response regulation (50).

N-3 and n-6 PUFAs are crucial structural constituents of the skin, as they are found in phospholipids, triglycerides, ceramides and as free fatty acids (51). When present in phospholipids, PUFAs influence the physical properties of biological

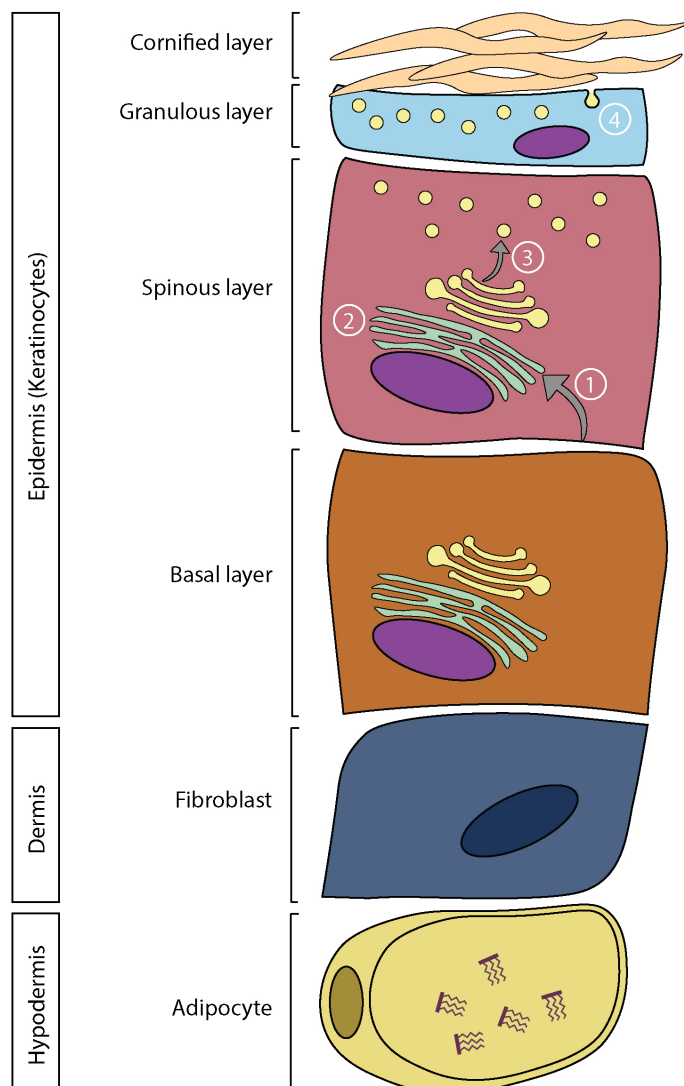
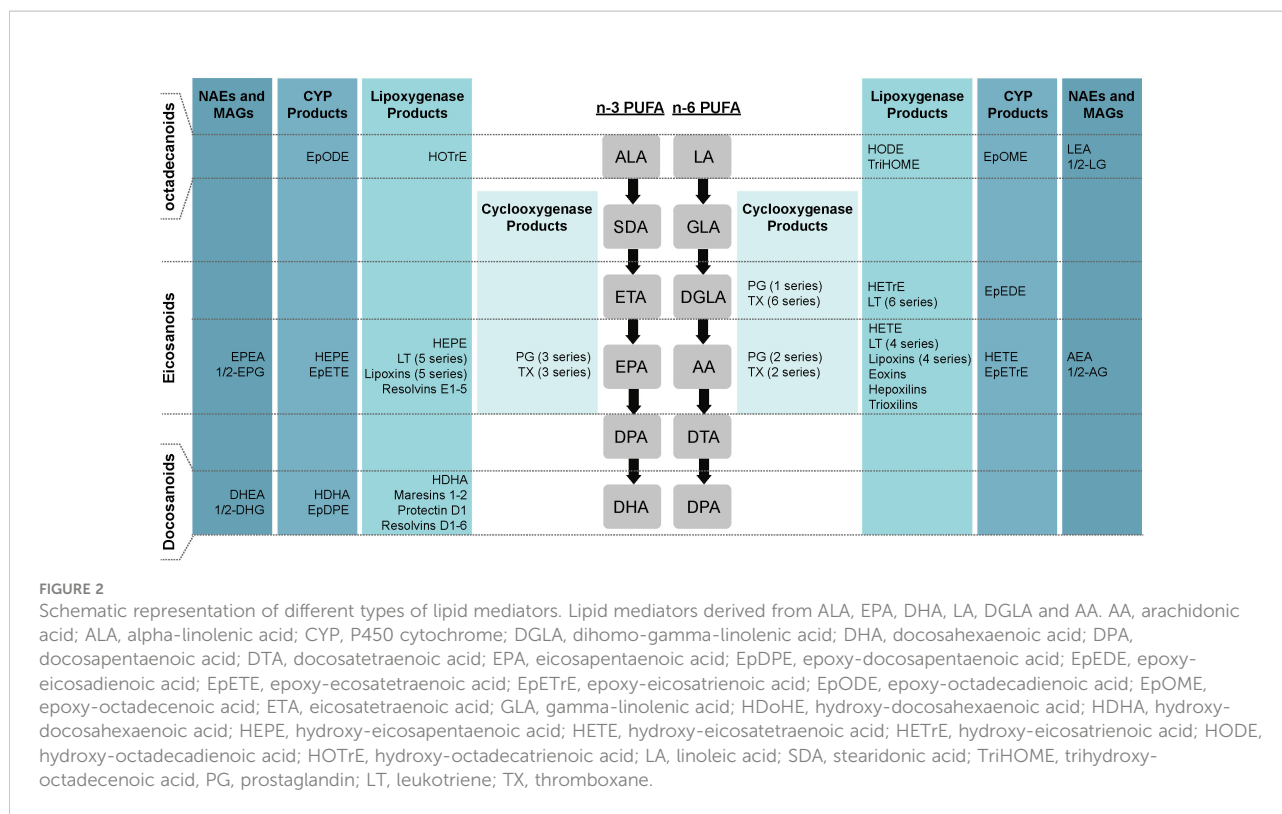


FIGURE 1
 Skin structure and lipid metabolism. In the epidermis: 1) Fatty acids are hydrolyzed from phospholipids and transported in the endoplasmic reticulum. 2) Synthesis of more complex lipids. 3) Storage of lipids in lamellar bodies. 4) Extrusion of lamellar bodies and organization of the lipid matrix.

membranes and modulate membrane organization, ionic permeability, elasticity, and microdomain formation (52). Indeed, when the level of unsaturation of fatty acids increases, the lipid membrane organization is affected, resulting in increased phospholipid membrane fluidity. The membrane fluidity induced by PUFAs is known to interfere with various receptors, such as insulin and T-cell receptors (48). LA alone accounts for 15% of fatty acids in the epidermis, while AA, EPA, and DHA account for 5% (11). The importance of LA for skin barrier formation has been extensively investigated over the years (53). The main symptom of dietary linoleic acid

deficiency in rodent is a drastic increase in skin permeability and the appearance of scaly patches (1, 54). Histologically, a deficiency in LA results in thickening of the skin (acanthosis) and a decrease in the thickness of the granular and cornified layers. Moreover, although lamellar bodies are synthesized normally, they are practically empty of content. Hence, their extrusion does not adequately fill the intercellular spaces (55). Furthermore, LA is used to produce ω -hydroxylated ceramides, essential for the scaffolding of the skin lipid matrix (36). The lack of ω -hydroxylated ceramides does not allow the organization of the lamellar bilayer, thus causing a



disorganization of the stratum corneum and a decrease in its impermeability.

Bioactive lipid mediators

A wide range of bioactive lipid mediators can be produced from the oxygenation of the free form of ALA, EPA, DHA, LA, DGLA, and AA by cyclooxygenases (COXs), lipoxygenases (LOXs), cytochrome P450 (CYP), or non-enzymatic reactions (Figure 2) (56). Specifically, COXs allow the generation of prostanoids, including prostaglandins (PGs), prostacyclins and thromboxanes (TXs). LOXs convert PUFAs into hydroxy-fatty acids (HFAs), leukotrienes (LTs), eoxins, lipoxins (LXs), trioxilin, hepoxilins, resolvins (Rvs), protectin (PD) and maresins (MaRs). CYP converts PUFAs to other types of HFAs and to epoxygenated FAs (EET). PUFAs can also be oxidized to an array of lipid mediators following non-enzymatic reactions, such as to isoprostanes (57, 58). Finally, other lipid mediators can also be produced from phospholipids that contain PUFAs, such as endocannabinoids, N-acyl ethanolamines (NAEs) and monoacylglycerols (MAGs) (59). Bioactive lipid mediators can also be classified according to the number of carbons they contain. Lipid mediators with 18 carbons (ALA- and LA-derived), 20 carbons (EPA-, DGLA-, and AA-derived) and 22 carbons (DHA-derived) are named octadecanoids, eicosanoids and docosanoids respectively (2). AA-derived

eicosanoids are usually present in the greatest quantities and are therefore more studied in the literature. Indeed, recent lipidomic analyses have shown that AA-derived eicosanoids alone account for nearly half of all bioactive lipid mediators (2).

Prostanoids

Prostanoids are generated by COX types 1 (COX1) and 2 (COX2). COX1 is a constitutive enzyme producing basal levels of prostanoids, while COX2 is a non-constitutive enzyme, and its expression is modulated by external stimuli to regulate inflammatory responses (60). COXs convert EPA, DGLA and AA into PGH, which is subsequently transformed by the various prostaglandin synthases into PGE, PGD, PGF, PGI, TXA and TXB. EPA, DGLA and AA are respectively metabolized into series 3, series 1 and series 2 prostanoids (61). Prostanoids are characterized by their 5-carbon ring structure (2). They regulate a wide variety of mechanisms primarily through their binding to specific prostanoid receptors. These GPCRs are divided into five classes based on their affinity for PGD, PGE, PGF, PGI or thromboxanes, namely DP, EP, FP, IP, and TP receptors respectively. EP receptors are divided into four subtypes, namely EP1, EP2, EP3 and EP4. DPs are divided into two subtypes: DP1 and DP2 (62).

The broad understanding of prostanoid metabolism is attributable to the 1970s discovery that COXs are therapeutic targets of aspirin (63). Prostanoids have been widely studied ever since and it has emerged that at low concentrations, they

regulate skin biological processes, whereas at high concentrations, they regulate inflammatory responses (64). AA-derived PGE₂ is one of the major eicosanoids produced in the skin by both fibroblasts and keratinocytes, and it is one of the most studied prostanoids (65–67). PGE₂ is involved in the regulation of the proliferation and differentiation of epidermal keratinocytes (68, 69). Moreover, PGE₂ has vasodilatory properties, can regulate the migration and maturation of Langerhans cells and was found to be involved in skin aging (70–72). PGF_{2α} and PGD₂ are also major PGs found in the skin (73). The series-3 prostanoids also bind to the various prostanoid receptors, but with less affinity than the series-2 prostanoids. Consequently, their individual role has been little studied since it is assumed that they exert similar functions to their n-6-derived congeners.

Hydroxy-fatty acids and leukotrienes

LOXs can generate a complex and elaborate network of bioactive lipid mediators beginning with the generation of mono-, di- or tri-HFAs (Figure 3) (2). They are classified according to the position of oxygen insertion in the PUFA, namely 5-LOX, 8-LOX, 9-LOX, 11-LOX, 12-LOX, and 15-LOX (74). There are two

isoforms of 15-LOX, 15-LOX-1 and 15-LOX-2, and two isoforms of 12-LOX. LOXs transform ALA into hydroxy-octadecatrienoic acids (HOTrEs), EPA into hydroxy-eicosapentaenoic acids (HEPEs), DHA into hydroxy-docosahexaenoic acids (HDHAs) (Figure 4), LA into hydroxy-octadecadienoic acids (HODEs), DGLA into hydroxy-eicosatrienoic acids (HETrEs) and AA into hydroxy-eicosatetraenoic acids (HETE) *via* their respective unstable peroxidized forms (HpOTrE, HpEPE, HpDHA, HpODE, HpETrE, and HpETE) (75). Keto derivatives (oxo) can then be produced *via* peroxidases from the HFAs (oxo-OTrEs, oxo-EPEs, oxo-DHAs, oxo-ODEs, oxo-ETrEs, oxo-ETEs) (2). Of note, some HFAs such as AA-derived 11-HETE, DHA-derived 13-HDHA and LA-derived 9-HODE can also be synthesized by COXs. However, these biosynthetic pathways are secondary (76, 77). PUFAs can also be transformed by LOXs into LTs, hepxilins and eoxins (2). Indeed, EPA-derived 5-HpEPE, DGLA-derived 5-HpETrE, and AA-derived 5-HpETE, can be converted by 5-LOX activating protein (FLAP) into LTs of the 5-, 6-, and 4-series respectively (78). First, hydroperoxy-FAs are transformed into LTAs, which are converted to LTBs by LTA₄ hydrolase (LTA₄H) or to LTC, LTD, and LTE by successive conversions of LTC₄ synthase (LTC₄S), gamma-glutamyltransferase, and dipeptidase (2). The LTs can be divided into two main groups, one composed of

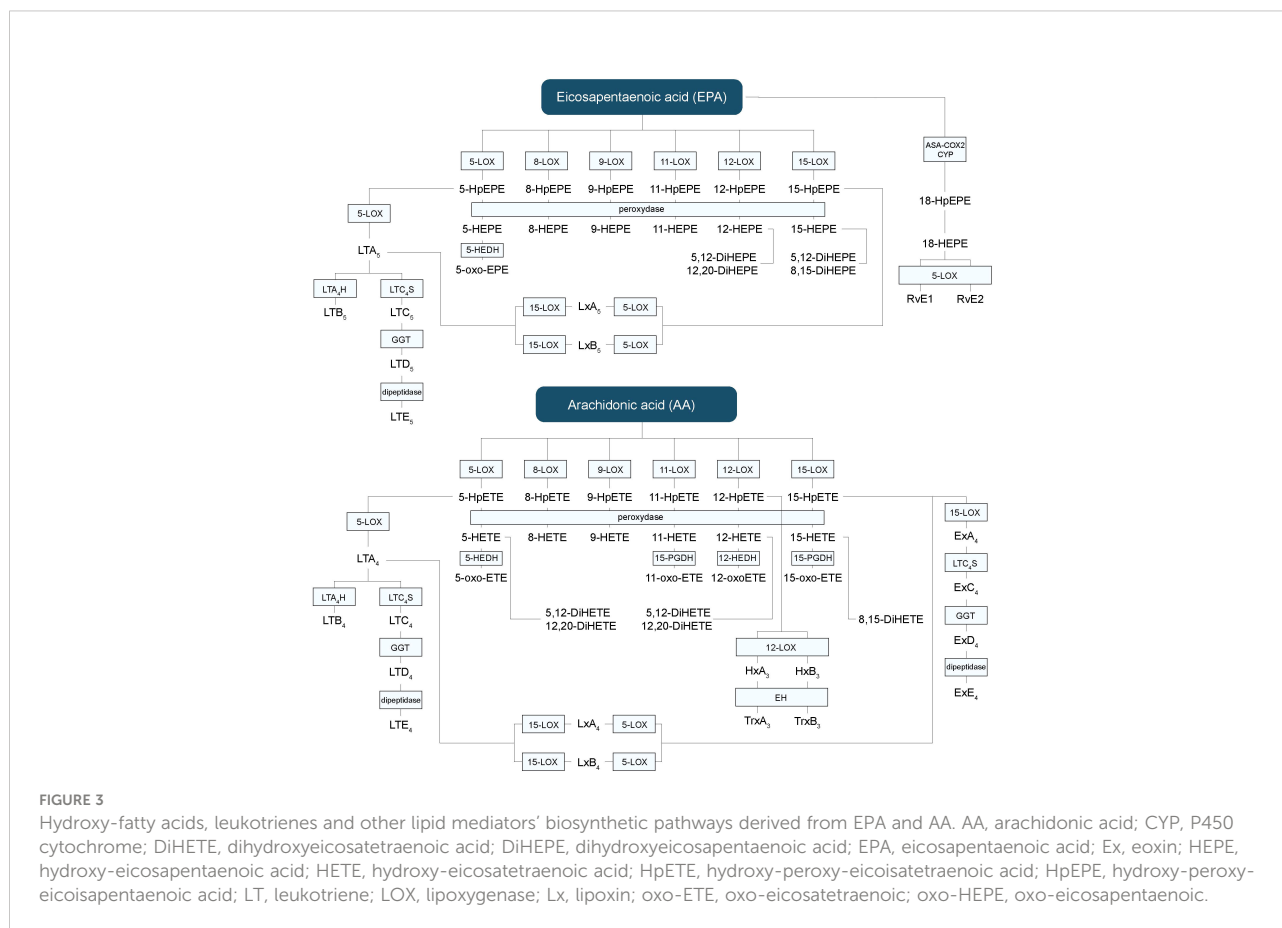
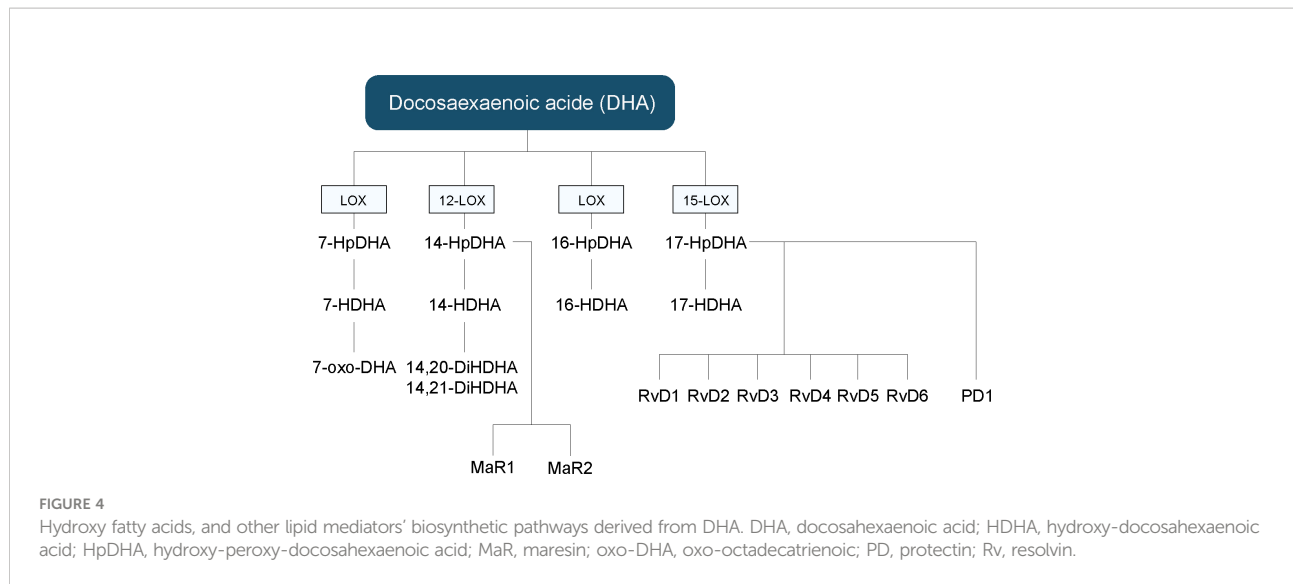


FIGURE 3 Hydroxy-fatty acids, leukotrienes and other lipid mediators' biosynthetic pathways derived from EPA and AA. AA, arachidonic acid; CYP, P450 cytochrome; DiHETE, dihydroxyeicosatetraenoic acid; DiHEPE, dihydroxyeicosapentaenoic acid; EPA, eicosapentaenoic acid; Ex, eoxin; HEPE, hydroxy-eicosapentaenoic acid; HETE, hydroxy-eicosatetraenoic acid; HpETE, hydroxy-peroxy-eicoisatetraenoic acid; HpEPE, hydroxy-peroxy-eicoisapentaenoic acid; LT, leukotriene; LOX, lipoxygenase; Lx, lipoxin; oxo-EETE, oxo-eicosatetraenoic; oxo-HEPE, oxo-eicosapentaenoic.



LTB₄ only and the second one containing cystenyl LTs (Cys-LTs), i.e., LTC₄, LTD₄ and LTE₄ (Figure 3) (79). A leukotriene-like pathway is also taken by AA-derived 15-HpETE to form eoxins A₄, C₄, D₄, and E₄. The receptors activated by HFAs remain poorly understood. They are known to act as signaling mediators by activating GPCRs and to be ligands activating peroxisome proliferator-activated receptors (PPARs) (75). LTB₄ binds to high-affinity LTB₄ (BLT1) and low-affinity LTB₄ (BLT2) receptors (79). All Cys-LTs bind to CysLT1R, CysLT2R, and CysLT3R receptors (79).

HFAs and their derivatives are involved in the regulation of several biological processes, including skin homeostasis. In general, HFAs produced by 12-LOX are mostly associated with pro-inflammatory properties, whereas those derived from 15-LOXs are better known for their anti-inflammatory properties (73). In the skin, both 12- and 15-LOX are very active, and 12-LOX plays a key role in the regulation of cell survival (75, 80). 12-HETE is present in large quantities in the skin (81, 82). It is involved in the proliferation of epithelial cells and in the synthesis of dermal extracellular proteins (83, 84). Similarly, epidermal 15-LOXs produce significant levels of 15-HEPE, 13-HODE, 15-HETE and 17-HDHA (73). The production of 15-HETE by dermal cells decreases the growth of epidermal cells by reducing the expression of 12-LOX (75, 85). 13-HODE has antiproliferative properties in the epidermis (86). Of note, 12- and 15-LOX metabolism differs between humans and rodents. Indeed, leukocyte-type 12/15-LOX synthesizes both 12- and 15-HETE in rodents, unlike in humans, which might lead to different HFA profiles in mice (87). The level of activity of 5-LOX in the healthy skin is low and is mainly associated with differentiated keratinocytes, Langerhans cells, and leukocytes upon infiltration (88). Different enantiomers of HFAs may have different effects (89). 8-, 9- and 11-HETE are also found

in the skin (90). Finally, some HFAs can be incorporated into the phospholipids of cell membranes, including those of keratinocytes. Indeed, relatively high amounts of 15-HETE, 5-HETE, 9-HODE, and 13-HODE are found in the *sn*-2 position of phospholipids (91, 92). LTs are known for their inflammatory properties. Indeed, the BLT1 receptor is predominantly expressed on leukocytes, and its activation by LTB₄ is involved in the regulation of chemotaxis and the activation of these cells. Little is known about the effect of BLT2 receptor activation (79). Both receptors are also expressed in keratinocytes, but not in fibroblasts (93). Activation of the BLT2 receptor with an agonist induces the migration of keratinocytes and the stimulation of transforming growth factor-β1 (TGF-β1) production, thereby stimulating fibroblast proliferation (94). Series 5 LTs derived from n-3 PUFAs also exert inflammatory effects by activating the same receptors as those of series 4. However, their affinity for these receptors is 100-fold lower than for series 4 LTs, resulting in a lesser inflammatory effect (50).

Specialized pro-resolving mediators

PUFAs can be transformed by the LOXs into SPMs, including LX, Rvs, PD and MaRs (2). AA is converted to LXA₄ and LXB₄ (95). EPA is converted to 18-HEPE by acetylated COX-2 or CYP, as well as in RvE1-5, LXA₅ and LXB₅ (96, 97). DHA can be converted into PD1, MaR1, MaR2 and RvD1-6 (98, 99). The RvEs and RvDs are synthesized by the combined action of the 5-, 12- and 15-LOX. However, their exact biosynthetic pathways are still only partly defined. In the inflammatory process, RvE1 is known to bind to ChemR23 receptors to generate resolving responses, while RvD1 interacts with ALX/FPR2 and DRV1 in a context-specific manner (100, 101). RvE1 also binds to BLT1 and ERV1 receptors (96, 101, 102). RvD2 was shown to be a potent ligand for GPR18 also

known as DRV2 (103). Additionally, lipoxins exert their anti-inflammatory action by binding to the ALX receptor (104). LXA₄ can also serve as an endogenous ligand of the endocannabinoid receptor CB₁ (102, 105).

The main SPMs that were detected in healthy human skin are the RvD5 and MaR2 (90). Levels of other SPMs, such as RvE1, RvD1 or PD1 were not detected in human skin and plasma samples even after n-3 PUFA supplementation (106). The ALX/FPR2 and DRV2 receptors were found in the epidermal layer of human skin (107).

Endocannabinoids, monoacylglycerols and N-acyl ethanolamines

The discovery of CB₁ and CB₂ receptors led to the identification of endogenous molecules able to bind to these proteins, namely arachidonoyl-ethanolamide (AEA) and 2-arachidonoylglycerol (2-AG), both derived from AA (108, 109). 2-AG and AEA are the two classic endocannabinoids. AEA is part of the larger NAE family while 1- and 2-AGs are part of the MAG family (110). Over the past 15 years, many molecules from both families have been further characterized (111–113). Since these new mediators share similar functions with endocannabinoids, they have been grouped under the term endocannabinoidome (114, 115). NAEs can be biosynthesized through 4 pathways. The most studied pathway begins with the transfer of an acyl chain from a phospholipid to the primary amide of a phosphatidylethanolamine by calcium-dependent transacylase (CDTA) to form an *N*-acylphosphatidylethanolamine (NAPE). Then, a PLD hydrolyzes the NAPE to generate the NAE (116). MAGs are generated from a phospholipid that is hydrolyzed by phospholipase C to form a DAG, and then transformed to a MAG by DAGL. NAEs and MAGs are produced and then rapidly inactivated by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively (116). The effect of endocannabinoids is mediated by the activation of the cannabinoid receptors, CB₁ and CB₂, both expressed in the skin (117). Additionally, other less specific receptors can be stimulated by endocannabinoids such as Transient Receptor Potential Vanilloid-1 (TRPV1), 5-hydroxytryptamine (5-HT), PPAR γ , and PPAR α (118).

Although endocannabinoids are usually related to the stimulation of the nervous system, recent evidence has shown that they may also have an important role to play in skin homeostasis (119, 120). The endocannabinoid signaling system is fully present in both keratinocytes and fibroblasts (121, 122). Both AEA and 2-AG are found in the dermis and the epidermis (56, 90, 106). The main NAEs found in the skin are the palmitoyl-ethanolamide, followed by steroyl-ethanolamide, oleoyl-ethanolamide, linoleoyl-ethanolamide, AEA, docosahexaenoyl-ethanolamide and eicosapentaenoyl-ethanolamide (123). Similarly, the predominant MAGs in the epidermis are the 2-palmitoyl-glycerol, followed by 2-oleoyl-glycerol, 2-linoleoyl-glycerol, 2-AG, 2-docosahexaenoyl-glycerol

and 2-eicosapentaenoyl-glycerol (90). Recently, two new molecules, namely 13-HODE-EA and 13-HODE-G, were characterized and identified in healthy skin (124, 125). The CB₁ receptor is located in the spinous and granular layers of the epidermis, as well as in differentiated cells of the sebaceous glands and hair follicles (117). The CB₂ receptor, on the other hand, is expressed in the basal layer of the epidermis as well as in undifferentiated cells of the sebaceous glands and hair follicles (126). The CB₂ receptor is also abundantly expressed in immune cells (127). TRPV1 receptors are expressed primarily in basal layer keratinocytes, but low levels of expression have also been observed in supra-basal layer keratinocytes (128). Endocannabinoids are thought to be involved in the regulation of the epidermal differentiation process (118, 129).

Psoriasis

Psoriasis is an autoimmune skin disease affecting about 3% of the worldwide population (130). This condition is characterized by the appearance of erythematous plaques covered with whitish scales (131). The severity of the disease varies significantly between individuals, leading to several classifications. According to the National Psoriasis Foundation, psoriasis is considered mild when less than 3% of the body surface is affected, moderate when 3 to 10% is affected, and severe when it affects more than 10%. The Psoriasis Area Severity Index (PASI) is a clinical tool commonly used to assess and classify severity (132). Psoriasis is a multifactorial condition associated with various comorbidities, the most common being psoriatic arthritis, which affects 5 to 20% of psoriatic patients (131). Other associated comorbidities include cardiovascular disease, metabolic syndromes, Crohn's disease, type 2 diabetes, obesity, cancer, and depression (133, 134). The exact mechanisms triggering psoriasis remain unknown (131), however, it is well established that a combination of environmental and genetic factors is involved. The most common environmental factors involved are skin infections, injuries or trauma, psychological stress, medications, alcohol consumption, and smoking (131, 133). No definitive effective cure for psoriasis has yet been identified. Treatment is therefore based on a wide range of therapeutic approaches, including topical treatments, phototherapy, and systemic and biological agents (135). The selection of therapy varies for each patient according to the course of the disease, the extent of the activity, the severity of symptoms, and the response to treatments. Approximately 75% of patients with psoriasis are adequately treated with topical treatments, the main ones reported being vitamin D₃ analogues (calcitriol, calcipotriol, tacalcitol et maxacalcitol) and retinoic acids (tazarotene) (131, 136). These therapies are usually prescribed as monotherapies or with the addition of topical corticosteroids such as betamethasone, fluocinonide, and hydrocortisone, especially when using

retinoids in order to reduce inflammation and irradiation (131, 132). Topical treatments, however, have limited effects when treating patients with moderate to severe psoriasis. Phototherapy or systemic drugs should be then considered (131).

The main histological features of psoriasis are hyperproliferation and the incomplete differentiation of epidermal keratinocytes, the infiltration of immune cells, and increased angiogenesis (130). Psoriatic keratinocytes in the basal and spinous layers of psoriatic skin hyperproliferate and cause epidermal hyperplasia, also described as acanthosis (137). While the epidermis of healthy skin is about 50 to 100 μ m thick, the epidermis of psoriatic patients can reach about 250 μ m in thickness (36, 138). The differentiation process of keratinocytes is also deregulated, resulting in the suppression of the stratum granulosum as well as the presence of undifferentiated keratinocytes in the stratum corneum (139). This abnormal differentiation of the psoriatic epidermis results in significant deregulation of the proteins of the stratum corneum. In general, proteins expressed in the early supra-basal layers of the epidermis, known as early markers of cell differentiation (involucrin and transglutaminase 1), are overexpressed, whereas proteins expressed in the later layers of the epidermis, the late markers (loricrin and filaggrin), have decreased expression (140). Dermal blood vessels are elongated in the papillary dermis region resulting in elongation of the dermal papillae (papillomatosis). In addition, the marked dilation of these blood vessels causes redness, which is noticeable in psoriatic skin lesions (130). A significant infiltration of immune cells is observed in both the dermis and the epidermis of psoriatic skin, and is mainly composed of macrophages, dendritic cells, and memory CD4⁺ T cells in the dermis, and of an increased quantity of CD8⁺ T cells in the epidermis. Neutrophils are also present in the stratum corneum (130).

Psoriasis immunopathogenesis

Although the pathogenesis of psoriasis remains unclear, compelling experimental evidence suggests a T-cell-based immunopathogenesis (131). Nevertheless, the involvement of both epithelial and immune cells is essential for the establishment of a psoriatic lesion (141–143). The first step is the activation of cutaneous innate immunity (Figure 5): environmental factors induce stress, which initiates the process of lesion formation in a patient with a predisposition to psoriasis. In response, keratinocytes secrete their own deoxyribonucleic acid (DNA), which forms complexes with antimicrobial peptides (141, 144). Keratinocytes also produce cytokines, including interleukin-1 β (IL-1 β), IL-6, and tumor necrosis factor- α (TNF- α), and chemokines such as CCL20, CXCL9, CXCL10, and CXCL11 (31). Then, keratinocytes stimulate cutaneous dendritic cells through the secretion of various inflammatory agents. Three types of dendritic cells are found in

the skin: the plasmacytoid dendritic cells, the myeloid dendritic cells of the dermis and the Langerhans cells of the epidermis. The DNA and antimicrobial peptide complexes secreted by keratinocytes activate plasmacytoid dendritic cells, which then produce interferon α (IFN- α) (145). In addition, cytokines secreted by keratinocytes and plasmacytoid dendritic cells induce the activation of myeloid dendritic cells in the dermis. These myeloid dendritic cells are antigen-presenting cells that provide the interface between innate and adaptive immunity, interacting with both CD8⁺ and CD4⁺ T cells. Then, the activation of adaptive immunity and of different types of T cells results in the formation of a complex signaling network composed of numerous cytokines and inflammatory mediators (31). The presentation of myeloid dendritic cell antigens to CD8⁺ T cells leads to their activation (141). The activation and expansion of CD8⁺ T cells causes their migration to the epidermis where they encounter major histocompatibility complex receptors present on the surface of keratinocytes, stimulating the local release of cytokines, such as IFN γ (141). These cytokines increase local inflammation and stimulate keratinocyte proliferation (31). In parallel, myeloid dendritic cells participate in the recruitment of CD4⁺ T cells by secreting additional pro-inflammatory mediators (IL-12, IL-23 and TNF- α), leading to the differentiation of naive CD4⁺ T cells into Th1 and/or Th17 T helper cells following antigen presentation (145). The differentiation of CD4⁺ T cells is specifically directed by cytokines secreted by the myeloid dendritic cells. In psoriasis, IL-12 and IL-23 production stimulates T cell differentiation into Th1 and Th17 cells, respectively, while few Th2 cells are observed (31). Hence, psoriasis adopts an immune profile characterized by Th1⁺, Th17⁺ and Th2⁻ cells. Th1, Th17, and Th22 cells produce signature cytokines of their own causing inflammation amplification loops (31, 141, 146). Th1 cells produce mainly IFN γ and TNF α , while Th17 cells produce IL-17A, IL-17F and IL-22. Over the past decades, research has put forward a key role for the IL-23/IL-17 axis within psoriasis. IL-17 stimulates keratinocytes to produce TNF α and chemokines (CXCL1, CXCL3, CXCL5, and CXCL8), which stimulate the recruitment of neutrophils to the lesion and induce the increased proliferation of keratinocytes (31). Th22 cells have recently been identified in psoriatic skin. IL-22 produced by Th17 and Th22 cells contributes to the psoriatic histological phenotype, including epidermal hyperplasia, acanthosis, and parakeratosis (132, 147, 148).

Lipid mediators dysregulated in psoriasis

The profound dysregulation of lipid metabolism in psoriatic skin has an impact on the levels of various structural lipids, such as phospholipids, triglycerides, and ceramides, and on the levels of lipids involved in inflammation, such as bioactive mediators (25, 149). Interestingly, a significant alteration of the metabolism of polyunsaturated fatty acids is found in psoriasis (Table 1). Indeed, a great abundance of n-6 PUFAs is measured in the

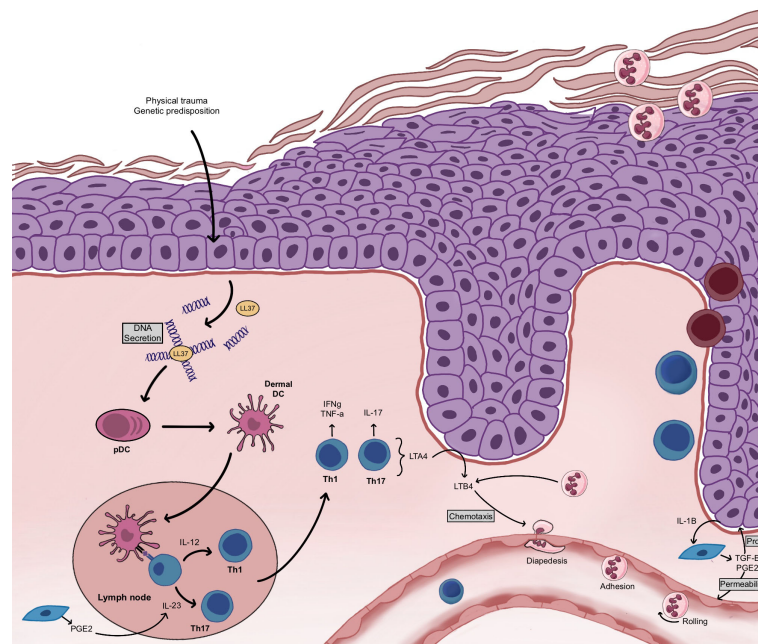


FIGURE 5

Establishment of the psoriatic plaque. Following a physical trauma or triggered by genetic predispositions, keratinocytes secrete their own DNA. The pDC become activated and stimulate the dermal DC. Dermal DC present their antigen to T cells, which induces T cell recruitment, CD4+ T cell polarization toward a Th1 and Th17 phenotype and CD8+ T cell migration to the epidermis. Keratinocytes enter into hyperproliferation. Neutrophils are recruited and migrate to the stratum corneum. LTB₄ contributes to neutrophil chemotaxis while PGE₂ contributes to keratinocyte proliferation.

blood and skin of these patients, which leads to altered levels of different types of bioactive mediators derived from n-6 PUFAs (25). AA is the n-6 PUFA that is the most dysregulated in psoriasis and many lipid mediators derived from it are found in highly increased amounts in psoriatic skin (Table 1) (26). These bioactive mediators play a key role as inflammatory mediators, contributing to the development of psoriatic lesions. The main AA-derived lipid mediators enhanced in psoriatic skin were reported to be the HFAs and their derivatives (167). Indeed, levels of 12-HETE were found to be increased in psoriatic skin (26, 167). 12-HETE is an important leukocyte chemoattractant and was found to promote T cell recruitment in psoriasis (168). However, finding increased amounts of 12-HETE in cutaneous wound healing prompted researchers to question whether 12-HETE production could also act as a defensive mechanism in psoriatic skin (169). Additionally, a strong increase in the quantities of LTB₄ were reported in the skin of patients with psoriasis. This lipid mediator would mainly be produced by infiltrating neutrophils, but T cells also have significant 5-LOX activity and keratinocytes considerable LTA₄H activity (170, 171). LTB₄ is present in both early and chronic plaques, supporting a role in the initiation of the disease (162). The signaling pathway of LTB₄-BLT1 in neutrophils significantly accelerates the infiltration of neutrophils in the skin in

collaboration with CXCR2, a chemokine receptor for CXCL1 and CXCL2, thus leading to psoriasis (172). LTB₄ also acts on dendritic cells and T cells through the BLT1 receptor and facilitates the migration and production of cytokines, thus contributing to the progression of psoriasis (173). Moreover, the topical application of LTB₄ to normal skin was found to induce microabscesses, and the hyperproliferation of epidermal cells (174, 175). Lower levels of 15-HETE were found in psoriatic dermis as compared with healthy dermis (176). Given the important role of 15-HETE in the regulation of 5- and 12-LOX epidermal activity, reduced levels of 15-HETE were postulated as being involved in the enhanced 5-LOX and 12-LOX product levels found in psoriasis (85). The levels of 9-HODE and 13-HODE were also found to be increased in psoriatic skin as compared with healthy skin (25, 177). It is important to mention that great differences were reported regarding the levels of certain lipid mediators depending on the source of the biological sample, i.e., whether it came from blood, serum, plasma or skin. Therefore, the study of these differences could lead to a better understanding of lipid dysregulation in psoriasis.

On the other hand, reports of prostanoid levels in psoriasis have been conflicting (25, 152, 167). Indeed, many research teams reported no alteration in PGE₂ levels in psoriatic skin as

TABLE 1 Summary of lipid mediators involved in psoriasis.

Markers	Biosynthesis	Receptors	Levels in psoriatic patients		Known mechanisms	References
			Blood	Skin		
Linoleic acid-derived lipid mediators						
9-HODE	12-LOX	TRPV1	Increased	Increased compared with healthy skin.	- Facilitates the release of inflammatory cytokines	(25, 150)
13-HODE	15-LOX	PPARs	Increased to double.	Increased compared with healthy skin.	ND	(25, 150, 151)
α-linolenic acid-derived lipid mediators						
9-HOTrE	12-LOX	ND	ND	Tends to increase in psoriasis compared with healthy skin.	ND	(25)
13-HOTrE	15-LOX	ND	ND	Tends to increase in psoriasis compared with healthy skin.	ND	(25)
Dihomo-γ-linolenic acid-derived lipid mediators						
PGE ₁	COX/PGES	EP1	Increased	Increased compared with healthy skin.	- Increases cAMP levels	(151, 152)
Arachidonic acid-derived lipid mediators						
PGE ₂	COX/PGES	EP2-EP4	No effect	Increased in the epidermis	- Increases the production of IL-23 by dendritic cells - Increases the expression of the IL-23 receptor gene on Th17 cells - Supports the expansion of Th17 cells - Stimulate keratinocyte proliferation	(25, 26, 153)
PGF _{2a}	COX/PGFS	FP	ND	Increased in psoriatic epidermis	ND	(26, 154)
8-iso-PGF _{2α}	Oxidative stress	ND	ND	Increased	-Activation of TNF α	(151)
15-d-PGJ ₂	CRTH2 and PPAR γ	ND	ND	Increased compared with healthy skin.	- Chemotaxis of Th2 cells, eosinophils, and basophils - Regulation of PPAR γ (particularly in macrophages) -Up-regulation of NF- κ B and ERK signaling pathways	(151, 155)
TXB ₂	TXs	TP	ND	Decreased compared with non-lesional skin	ND	(25, 151)
5-HETE	5-LOX	OXER1, BLT2	No effect	Slightly increased compared with healthy skin	- Activation of OXER1 receptor, resulting in cell-activation pathways such as MAPK, ERK, p38 and protein kinase B - Accumulation of monocyte-derived macrophage	(25)
8-HETE	8-LOX	PPAR α	ND	Increased compared with healthy skin.	ND	(25)
9-HETE	9-LOX	RXR γ	Slightly increased	No effect	- Chemoattractant of neutrophils	(25)
11-HETE	COX2	ND	Slightly increased	Slightly decreased compared with healthy skin	11R-HETE, generated by COX-2 in epithelial cells, is also a substrate for 15-PGDH, being converted to 11-oxo-EETE.	(25, 156)
12-HETE	12-LOX	BLT2	ND	Increased compared with healthy skin.	- PMN chemoattractant	(25, 26, 150, 157, 158)
15-HETE	15-LOX	BLT2	ND	Increased compared with healthy skin.	- Anti-apoptotic activities	(159)
4-HNE	ND	ND	Increased	Increased	- Activation of the MAPK pathway	(151)
LTB ₄	5-LOX	BLT1 > BLT2	No effect	Increased compared with healthy skin.	- Most potent neutrophil chemoattractant -Facilitates the migration of dendritic cells and T cells, as well as their production of cytokines	(25, 151, 153, 157, 160)
LTC ₄	5-LOX	CysLT2>CysLT1	ND	Increased compared with healthy skin.	- Most potent eosinophil chemoattractant	(157, 160, 161)
LTD ₄	5-LOX	CysLT1	ND	Increased compared with healthy skin.	ND	(160–162)
Eicosapentaenoic acid-derived lipid mediators						
5-HEPE	5-LOX	GPR119-GPR120	Slightly increased	No effect	ND	(154)

(Continued)

TABLE 1 Continued

Markers	Biosynthesis	Receptors	Levels in psoriatic patients		Known mechanisms	References
			Blood	Skin		
12-HEPE	12-LOX	GsPCR (not identified yet)	Increased	No effect	- Downregulation of CXCL1 and CXCL2 gene in keratinocytes	(154, 163, 164)
15-HEPE	15-LOX	PPAR γ	Increased	Slightly increased	- Diminution of the migration of peripheral mononuclear cells	(51, 154, 165)
18-HEPE	CYP450	ND	Slightly increased	No effect	- Repression of CXCR4 expression on lung melanoma cells - Diminution of macrophage activation	(154, 166)
Docosahexaenoic acid-derived lipid mediators						
4-HDHA	5-LOX	PPAR γ	No difference	No difference	ND	(25, 159)
14-HDHA	12-LOX	ND	Slightly increased.	Decreased compared with healthy skin.	ND	(25)
17-HDHA	15-LOX	DRV1/DRV2	ND	Increased compared with healthy skin.	ND	(25)

COX, cyclooxygenase; GPR, G protein-coupled receptor; HEPE, hydroxyeicosapentaenoic; HETE, hydroxyeicosatetraenoic; HDHA, hydroxy-docosahexaenoic acid; HNE, hydroxyonenal; HODE, hydroxy-octadecadienoic acid; HOTrE, hydroxy-octadecatrienoic acid; IL, interleukin; LOX, lipoxygenase; LT, leukotriene; ND, not documented; PPAR, Peroxisome proliferator-activated receptor; PGJ, prostaglandin J; PGE, prostaglandin E; RXR, retinoid X receptor; TRPV1, transient receptor potential vanilloid 1; TX, thromboxane.

compared with healthy skin (25, 152, 167, 178), while some teams found an increase in PGE₂ in the psoriatic skin (26). A decreased capacity to biosynthesize prostaglandins was measured in involved and uninvolved psoriatic epidermis (152). *In vitro*, the production of PGE₂ by fibroblasts leads to the production of IL-1, stimulating the proliferation of keratinocytes (179, 180). Moreover, the production of PGE₂ by fibroblasts promotes the production of IL-23 by dendritic cells, which supports the expansion of Th17 cells (181, 182). Thereafter, the production of PGE₂ by Th17 cells increases the expression of a sub-unit of the IL-23 receptor gene on Th17 cells *via* EP2 and EP4 receptors, facilitating the generation of Th17 cells *in vitro* (181, 182). More recently, the levels of lipid mediators derived from n-3 PUFAs were also documented as being altered in psoriatic skin (25). Among these, the levels of 7-, 14- and 17-HDHA were found to be increased in psoriatic skin as compared with healthy skin, with 14-HDHA having the most striking changes (25).

Finally, large amounts of reactive oxygen species (ROS) found in psoriasis can affect membrane phospholipids, leading to lipid peroxidation and the generation of reactive aldehydes, such as 4-hydroxynonenal (4-HNE). In fact, it was reported that 4-HNE and 8-isoPGF_{2 α} are up-regulated in psoriatic skin (151). Although the ratio of n-3 to n-6 PUFAs is already known to be greatly diminished in psoriatic skin, the amounts of n-3 PUFAs as well as their role in the establishment of psoriatic lesions has been poorly studied.

The lipid dysregulation observed in psoriasis could be the result of the altered expression of proteins involved in the biosynthesis of lipid mediators, as well as the inflammatory milieu engendered by psoriatic epithelial cells. Interestingly, in

various studies genes coding for different phospholipases have been listed as twenty of the most highly dysregulated genes in psoriasis (183). Protein analyses showed an increased number of different types of PLA₂ in psoriatic skin, according with the increase of the different lipid mediators measured in psoriatic skin (151). Other genes that are dysregulated in psoriatic skin include ALOX12B, which may be responsible for the increased amount of 12-HETE (78). *In vitro*, transcriptomic analyses comparing the genetic expression profile of healthy skin with that of the psoriatic substitutes produced by tissue engineering demonstrated the dysregulation of genes involved in lipid metabolism, particularly in the PUFAs of psoriatic patients (184). Most of the dysregulated genes in psoriasis have been reviewed elsewhere (185).

Effects of PUFA and bioactive lipid mediator interventions in psoriasis

n-3 PUFAs are known for their anti-inflammatory potential. However, their effectiveness is quite controversial despite the growing body of scientific data showing their beneficial effects. Clinical studies have investigated the effects of n-3 PUFAs, mainly EPA and DHA, on symptoms in psoriatic patients (Table 2). Several studies have shown that oral treatment with n-3 PUFAs improves the PASI score, erythema, scaling, itching, the extent of affected surfaces, and the amount of immune cell infiltration (187, 202, 203), whereas other studies have found no significant effects (191, 204).

In vitro and *in vivo* studies have investigated the mechanisms of action underlying the beneficial effects of n-3 PUFAs in

psoriasis (Table 2). The effectiveness of n-3 PUFAs on psoriasis was shown using a tissue-engineered psoriatic reconstructed skin model (205). The anti-psoriatic potential of ALA was investigated, showing that ALA reduces psoriatic keratinocyte proliferation by decreasing the production of pro-inflammatory lipid mediators (199). Similarly, DHA also alleviated the psoriatic features of the reconstructed psoriatic skin model, mainly by decreasing proliferation and improving the differentiation of psoriatic keratinocytes (201). Psoriasis is characterized by a strong increase in n-6-derived pro-inflammatory lipid mediators in the blood and lesional skin of patients (25). Therefore, in many studies the primary mechanism of action of an n-3 PUFA treatment is considered to be a decrease in these pro-inflammatory mediators through competition for enzymes in their metabolic pathway (199, 206). However, there is a lack of consensus among the various studies found in the literature. Additionally, n-3 PUFAs seem to affect the immune system (34). Indeed, ALA was showed to affect T cell functions in the reconstructed psoriatic skin model, mainly by decreasing the production of inflammatory cytokines (200). The impact of n-3 PUFAs on the adaptive immunity have also been studied in other models. Studies in humans have shown that dietary supplementation with fish oils decreases the relative percentage of CD4+ cells in peripheral blood, resulting in a decreased immune response (207). Moreover, a diet rich in n-3 PUFAs can reduce the expression of the class II histocompatibility major complex (CMH-II) on dendritic cells and other antigen-presenting cells, thus diminishing the likelihood of stimulating CD4+ cells (208). These studies also showed that the pre-treatment of endothelial cells with DHA decreases the functional adherence of T cells to endothelial cells *in vitro* (208, 209). Additionally, a high level of consumption of n-3 PUFAs was reported to reduce the production of TNF- α , IL-4, IL-6 and IL-1 β (207, 210). Otherwise, n-3 PUFAs can activate nuclear receptors, such as the PPARs, which intervene in the regulation of the transcription of many genes involved in the metabolism of lipids (207). EPA and DHA are also recognized as interrupting the autocrine IL-2 pathway (211). PPAR γ may inhibit the nuclear factor of activated T cells and could thus decrease the production of IL-2 (212). Finally, the polarization of CD4+ T cells into either Th17 or regulatory T cells (Treg) is partly governed by PPAR γ activity (213). Honda et al. suggested that PGE₂ produced by fibroblasts promotes the development of psoriatic dermatitis through the regulation of the IL-23 and IL-17 pathways. Therefore, a diet rich in n-3 PUFAs could directly alter those pathways by diminishing the production of PGE₂ (153). In IMQ-induced psoriatic FAT-1 mice, increased n-3 PUFA production was associated with a significantly reduced number of Th17 cells, and an increased number of Tregs in the spleen (214). Of note, FAT-1 mice are genetically modified mice capable of producing n-3 PUFAs from n-6 PUFAs since they have been engineered to express the *C.elegans* n-3 fatty acid desaturase gene (*fat-1*), thus

increasing the levels of n-3 PUFAs without the need for oral supplementation (214). However, PGE₂ seems to be a limited therapeutic target in the treatment of psoriasis. Indeed, non-steroidal anti-inflammatory drugs such as aspirin already target prostaglandin biosynthesis, *via* cyclooxygenase inhibition. Unfortunately, these drugs does not resolve immune-mediated disorders on their own, making them suboptimal for psoriasis treatment (215). Recent studies have also investigated the specific effects of bioactive lipid mediators (Table 2). Treatment by subcutaneous injection of 1 mmol/L of 15-HETE was shown to be effective, reducing the extent of plaques of two out of 13 patients with psoriasis (157). In 2018, Sawada et al. reported that the administration of RvE1 in an imiquimod-induced mouse psoriatic model inhibits the production of IL-23 by dendritic cells and accordingly decreases psoriatic features (173). It has also been shown that RvD3 reduces acute pain and itch in mice in the context of psoriasis (198). Additionally, the administration of RvE1 strongly inhibits the expression of IL-23 and IL-17 in psoriatic skin (216). Finally, phototherapy, including ultraviolet B (UVB) and psoralen ultraviolet A (PUVA), has been widely used to treat psoriatic lesions (217). Interestingly, the mechanism underlying phototherapy may involve lipid mediator signaling. Indeed, UVB, UVA and PUVA all decreased 12-LOX expression and increased 15-LOX expression in keratinocytes (158).

Interestingly, n-3 PUFAs also seem to possess therapeutic potential in other pathologies and comorbidities related to psoriasis, including atherosclerosis (218). In fact, the positive effects of EPA on inflammatory diseases have been put forward in the Reduction of Cardiovascular Events with Isopent Ethyl-Intervention Trial (REDUCE-IT). This study showed that the daily consumption of 2 g of EPA ethyl ester by patients with established atherosclerosis heart disease was associated with an absolute 4.8% reduction in cardiovascular events (8). Similar to statins, n-3 PUFAs were shown to have pleiotropic effects and to attenuate the atherogenic response (219). Moreover, hypertriglyceridemia, which is characterized by a severe elevation of triglyceride levels and is associated with obesity, can be partially reduced with the consumption of 4 g/day of EPA and DHA (220). It is also important to mention that the n-3 PUFA index, which measures the percentage of long-chain n-3 PUFAs EPA and DHA in red blood cell membranes, greatly influences an individual's response to dietary n-3 PUFA supplementation. Indeed, individuals with lower n-3 PUFA baseline before the oral supplementation tend to respond better to the n-3 PUFA supplementation than those with a naturally high baseline (221, 222).

Conclusion

In conclusion, the roles of n-3 and n-6 PUFAs in the skin are numerous and complex. This study summarizes current findings

TABLE 2 Summary of studies examining the effect of PUFA interventions in psoriasis.

PUFAs or lipid mediators	Clinical trials or pre-clinical study models	Treatments	Effects	References
Human clinical trials				
ALA	Human clinical trials	2600 mg ALA (12 weeks)	Significant clinical improvement of the PASI	(186)
EPA	Human clinical trials	180 mg (12 weeks)	↓ itching after 12 weeks.	(187)
15-HETE	Human clinical trials	Subcutaneous injection of 1 mmol/L of 15-HETE	↓ extent of plaques of two out of 13 patients	(157)
EPA-DHA	Human clinical trials	1200-1800 mg (8 weeks)	↓ erythema and skin scaling	(188)
		2400-3600 mg (15 weeks)	↓ body surface area of psoriasis	(15)
		15% EPA and 10% DHA (4 weeks)	↓ erythema and desquamation in patients	(189)
		2100-21000 mg (2 weeks)	Moderate improvement in clinical manifestations	(190)
			↓ disease severity	
		320-510 mg (16 weeks)	↓ scaling and redness	(191)
			↓ cellular infiltration.	
		132-240 mg (36 weeks)	No significant effects	(192)
		80-650 mg (4 weeks)	↓ scalp lesion, target plaque erythema lesion, infiltration, and scaling	(193)
	1800 mg (12 weeks)	↓ PASI, erythema, duration, scaling, and extent of area involved	(194)	
Animal models				
RvE1	Imiquimod-induced psoriasis mice model	Intravenous administration of 200 ng per mouse 30 min before IMQ application	↓ epidermal hyperplasia ↓ IL-23 mRNA expression ↓ IL-23 production by dendritic cells <i>in vitro</i> ↓ migration of cutaneous DCs and $\gamma\delta$ T cells	(173)
MaR1	Imiquimod-induced psoriasis mice model	Topical application of 100 ng per ear 30 min prior IMQ application each day for 5 consecutive days	↓ ear swelling response ↓ IL-17A production by $\gamma\delta$ TCR ^{mid+} and CD4+ cells ↓ IL-23 receptor by suppressing ROR γ t	(195)
PD1	Imiquimod-induced psoriasis mice model	0.01-1 μ g/kg injected subcutaneously for 7 consecutive days	↓ skin thickness, redness and scaling ↓ IL-1 β , IL-6, IL-17 and CXCL1 mRNA expression ↓ STAT1 and NF- κ B signaling pathway ↓ CD4 ⁺ IFN- γ ⁺ IL-17 ⁺ T lymphocytes	(196)
RvD1	Imiquimod-induced psoriasis mice model	Intraperitoneal administration of 1-5 μ g/kg 1h prior to IMQ application	↓ IMG-induced psoriasisform dermatitis ↓ IMG-induced activation of ERK1/2, p38, JNK and NF- κ B	(197)
RvD3	Imiquimod-induced psoriasis mice model	Single and repeated systemic administration. 2.8 mg/kg	↓ TRPV1-dependent acute pain and itch in mice	(198)
In vitro models				
ALA	Human reconstructed psoriatic skin model	10 μ M	↓ keratinocyte proliferation ↑ keratinocyte differentiation (increased late differentiation markers such as filaggrin) ↑ ERK1/2 phosphorylation	(199)
	Human reconstructed psoriatic skin model with T cells	10 μ M	↓ keratinocyte proliferation ↑ keratinocyte differentiation ↓ T cell migration in the epidermis ↓ inflammatory cytokines and chemokines (CXCL1, IL-6, IL-8)	(200)
DHA	Human reconstructed psoriatic skin model	10 μ M	↓ keratinocyte proliferation ↑ keratinocyte differentiation ↓ TNF- α , COX2 and PPAR δ ↑ PPAR γ	(201)

↑ Increased; ↓ Decreased.

ALA, alpha-linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HETE, hydroxyeicosatetraenoic; MaR, maresin; NSAIDs, non-steroidal anti-inflammatory drugs; PASI, psoriasis area and severity index; PD1, protectin D1; Rv, resolvin.

on the implication of n-6 and n-3 PUFA lipid mediators in the skin and more precisely, their involvement in psoriasis. Findings on new bioactive lipid mediators are gradually being reported, however the underlying mechanisms have yet to be revealed. The dietary intake of n-3 and n-6 PUFAs greatly influences skin homeostasis, both in healthy and psoriatic skin. Recent advances have shown the potential of n-3 PUFAs as a treatment for psoriatic patients, notably in the reduction of the production of pro-inflammatory cytokines and the alteration of T cell functions, as well as in the reduction of the formation of inflammatory bioactive lipid mediators. Thus, deepening knowledge on the role of n-3 PUFAs in psoriasis may lead to the discovery of novel therapeutic targets for the disease.

Author contributions

Conceptualization, MS, SM, ZR, and RP. Visualization, MS. Formal analysis, MS. Data curation, MS, SM, ZR, and RP. Writing—original draft preparation, MS, SM, and ZR. Writing—review and editing, MS, SM, ZR, and RP. Supervision, RP. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

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