Healing fats of the skin: the structural and immunologic roles of the ω-6 and ω-3 fatty acids
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Abstract Linoleic acid (18:2ω6) and α-linolenic acid (18:3ω3) represent the parent fats of the two main classes of polyunsaturated fatty acids: the ω-6 (n-6) and the ω-3 (n-3) fatty acids, respectively. Linoleic acid and α-linolenic acid both give rise to other long-chain fatty acid derivatives, including γ-linolenic acid and arachidonic acid (ω-6 fatty acids) and docosahexaenoic acid and eicosapentaenoic acid (ω-3 fatty acids). These fatty acids are showing promise as safe adjunctive treatments for many skin disorders, including atopic dermatitis, psoriasis, acne vulgaris, systemic lupus erythematosus, nonmelanoma skin cancer, and melanoma. Their roles are diverse and include maintenance of the stratum corneum permeability barrier, maturation and differentiation of the stratum corneum, formation and secretion of lamellar bodies, inhibition of proinflammatory eicosanoids, elevation of the sunburn threshold, inhibition of proinflammatory cytokines (tumor necrosis factor-α, interferon-γ, and interleukin-12), inhibition of lipoygenase, promotion of wound healing, and promotion of apoptosis in malignant cells, including melanoma. They fulfill these functions independently and through the modulation of peroxisome proliferator-activated receptors and Toll-like receptors.

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Introduction

Interest in the use of dietary fats to treat skin disease is marked by the historic study of Burr and Burr in 1929,1,2 where rats fed a diet devoid of all fat experienced growth retardation, reproductive failure, and a scaling erythematous skin eruption with increased transepidermal water loss. Clinical manifestations diminished when the diet was supplemented with linoleic and α-linolenic acids. Similarly, one of the investigators from these early experiments found he could rid his hand dermatitis by consuming these polyunsaturated fatty acids (PUFAs). Originally referred to as vitamin F, these fats soon came to be known as the essential fatty acids (EFAs), because humans lack the enzymes necessary for their synthesis.

These original works, as well as other early studies, have been criticized because a distinction was not drawn between supplementation with ω-6 (linoleic acid) or ω-3 (α-linolenic) fatty acids.3 Differentiating between the two is important, because their roles, as we have now come to understand more clearly, are distinct—linoleic acid and its products serve as structural precursors for the important stratum corneum ceramides, and α-linolenic derivatives serve as immune modulators. We have just begun to recognize the sophisticated contribution of the PUFAs in skin disease through these and other structural and immunologic roles.

As we shall discuss, linoleic acid (LA) and its derivatives play a central role in the structure and function of the stratum corneum permeability barrier, defects of which are most
notable in atopic dermatitis. Derivatives of ω-linolenic acid (ALA) can modulate the immune response of the epidermis by influencing T lymphocytes, acting on Toll-like receptors (TLRs), and activating caspase cascades that influence many inflammatory dermatoses, including acne vulgaris, psoriasis, atopic dermatitis, systemic lupus erythematosus, and skin cancer. Finally, the ω-3s are ligands for an important class of transcription factors, the peroxisome proliferator-activated receptors (PPARs), which are important in lipid metabolism, sugar homeostasis, and insulin sensitization as well as inflammation, immune regulation, and skin barrier homeostasis. They also show promise as natural options for treating inflammatory skin disease and skin carcinogenesis, including melanoma.

**PUFA terminology, metabolism and dietary homeostasis**

LA (18:2ω6) and ALA (18:3ω3) represent the parent fats of the two main classes of PUFAs: the ω-6 (n-6) and the ω-3 (n-3) fatty acids, respectively. LA and ALA both give rise to other long-chain fatty acid derivatives and a host of other lipid mediators, including prostaglandins, leukotrienes, and lipoxins by way of a shared set of enzymes (Figure 1).

LA is found in the oils of safflower, grape seed, poppy seed, sunflower, hemp, corn, wheat germ, cottonseed, and soybean. Many of these oils are commonly found in baked goods and infant formula. ALA is a component of green leafy vegetables, flax seed, walnuts, soybean, and canola oils. Their derivatives, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are obtained through breast milk and the oils of cold-water fish such as salmon, mackerel, sardines, herring, and rainbow trout.4 The ideal homeostatic cellular concentration of ω-6:ω-3 is 3:1.5,6 Many barriers exist to achieving this level, including:

- **Western diets.** The intake of ω-6 fats is approximately 10 times greater than ω-3 fats. Furthermore, as a result of food processing and cooking, many ω-3 fats are lost or oxidized.7
- **Enzyme competition.** Both classes depend upon the same enzymes for the production of their long-chain derivatives. Given the abundance of ω-6s in the diet, EPA and DHA are minimally produced; therefore, a balanced ratio of these fats is dependent on nutritional intake.

In addition, production of long-chain derivatives is minimal due to the following:

- **Inefficiency of Δ5 and Δ6 desaturase enzymes.** The production of long-chain derivatives of LA and ALA is dependent on these enzymes, but the process is quite inefficient, where only 5% to 10% of ALA is converted to EPA and 1% to DHA.8 Infants are even less capable of converting these fats due to immature enzyme activity and are dependent on dietary supply through breast milk.

- **Western diet and disease.** Saturated fats, trans-fats, fat-free diets, glucose-rich diets, alcohol, glucocorticoids, reduced insulin levels, protein deficiency, hypothyroidism and age also reduce the activity of the desaturase enzymes.

What can be concluded is that extradietary supplementation of ω-3s is necessary to achieve a balanced ratio of ω-3:ω-6 fatty acids, especially in the cases of formula feeding, reduced cold-water fish intake, abundant alcohol consumption, diabetic states, protein deficiency, and aging.

Laboratory evaluation of EFA profiles can be obtained. Tissues preferentially metabolize PUFAs in this order: ω-3 > ω-6 > ω-9. An elevated mead acid (20:3ω9) level suggests a reduced blood level of ω-3 and ω-6 fatty acids, or essential fatty acid deficiency.3 When LA and ALA are not supplied by the diet, oleic acid (18:1ω9) serves as the substrate for PUFA generation, creating mead acid. As we will come to appreciate, ALA and LA are not easily replaced; conversely, they are vital to healthy skin.

**LA and the stratum corneum permeability barrier**

LA is the most abundant fatty acid in the epidermis. Importantly, it is also the precursor to ceramides, a major component of the extracellular lipid matrix that forms the stratum corneum permeability barrier (SCPB). There are essentially three components of the SCPB: the extracellular lipid matrix, the cornified envelope, and dense keratin fibrils aggregated by filagrin. The extracellular lipid matrix is composed of 50% ceramides, 25% cholesterol, and 15% free fatty acids.9 Lipids, enzymes, and antimicrobial peptides (β-defensin 2) are packaged into lamellar bodies in the upper stratum spinosum and stratum granulosum.10 Extrusion of lamellar bodies into the extracellular space signals the cross-linking of the cornified envelope proteins loricrin, involucrin, and trichohyalin by trans-glutaminase. The extracellular lipid matrix coats the cornified envelope proteins, forming a strong, water-impermeable lamella.

Defective SCPB results when mutations occur in the proteins and enzymes that are important in this complex process11,12 or when lipid levels are reduced. Monounsaturated and saturated fatty acids can be synthesized within the epidermis. PUFAs must be obtained from the diet. Labeling experiments have shown that dietary fatty acids and cholesterol are delivered to the stratum corneum.13-16 Fatty acid transport proteins present in keratinocytes are more selective for PUFAs than monounsaturated fatty acids. When dietary PUFA is deficient, oleic acid takes its place, resulting in abnormal stratum corneum permeability and appearance.17-20 Insufficient LA also yields less ω-hydroxyeceramide, an important anchoring lipid connecting the extracellular lipid matrix to the skin.
cornified envelop. Therefore, PUFA insufficiency results in increased transepidermal water loss.\textsuperscript{21} Proliferative keratins (K6 and K16) and inflammation-associated keratins (K17) are also induced as a result of PUFA deficiency.\textsuperscript{22} These findings highlight the necessity of dietary fatty acids, especially $\omega$-6 fats, in epidermal homeostasis and the SCPB.\textsuperscript{23}

### SCPB and healthy skin

An acid environment is critical for the functioning of acid sphingomyelinase and $\beta$-glucocerebrosidase involved in the production of ceramides. This is facilitated by the catabolism of filaggrin, which yields the polycarboxylic acids pyrrolidine carboxylic acid and trans-urocanic acid\textsuperscript{24} that help maintain an acidic pH. They are also components of natural moisturizing factor that helps hydrate the stratum corneum. We have just reviewed the importance of dietary PUFA in maintaining the integrity of the SCPB.

Topically applied biologic lipids can also be effective in restoring the SCPB. More specifically, youthful skin is more dependent on a lipid-dominant mixture; whereas, a cholesterol-dominant mixture is required by aged skin.\textsuperscript{25} Use of statins in elderly patients may exacerbate xerosis, because topical lovastatin resulted in barrier irregularities and hyperproliferation of the epidermis.\textsuperscript{26} Other nutritional agents that stimulate ceramide synthesis and promote a healthy permeability barrier are listed in Table 1.\textsuperscript{26-32}

### SCPB and atopic dermatitis

Defects in the epidermal barrier are at the forefront of atopic dermatitis (AD). Defects in filaggrin have been established in patients with AD.\textsuperscript{33} Filaggrin is essential for the aggregation of keratin filaments in the outer stratum corneum and for providing the acid derivatives necessary to activate the production of ceramides. Not all patients with
expression in cultured keratinocytes.35 Cytokines in AD, have been shown to reduce filaggrin gene expression,34 arguing for defects in immunity in AD as ichthyosis vulgaris do not maintain the same degree of inflammation,34 thus suggesting that a defect in the Δ-6 desaturase enzyme was at work. Many reviews showed a benefit,41 but some were not as promising.42 The most recent meta-analysis on this issue showed that evening primrose oil is effective in a subset of patients with atopic dermatitis and elevated immunoglobulin (Ig) E levels.43

AD, biologic lipids, and other nutrients

Many current treatments for AD are effective at reducing inflammation and improving the texture of the skin, but they may also be hampering maturation of the skin barrier, creating a cycle of disease. For instance, bleach baths, although helpful in reducing the burden of Staphylococcus aureus on the skin surface, are likely preventing both acid sphingomyelinase and β-glucocerebrosidase that require an acid pH from producing ceramides. Colonization with ceramidase-producing Pseudomonas aeruginosa can also reduce ceramide levels in some patients.44,45

The enzymes involved in lipid uptake and synthesis are up-regulated during acute barrier disruption and cholesterol synthesis is increased.46,47 Acetyl coenzyme A carboxylase and fatty acid synthase, needed for de novo fatty acid synthesis, are enhanced.48,49 Fatty acid transport proteins are increased.50 Production of epidermal fatty acid-binding protein is also increased.51-54 If ample lipid can be supplied to the epidermis, exogenous acids or enzyme sources may help convert these fats into ceramides. The topical application of a cream containing the lactic acid bacterium Streptococcus thermophilus increased concentrations of ceramides after a 2-week application, with improvement in erythema, scaling, and itch.55

Healing of the SCBP after acute barrier disruption is also dependent on a graded calcium concentration from the stratum granulosum to the stratum corneum. Occlusive petrolatum, although seemingly controlling transepidermal water loss, impedes the calcium concentration gradient and prevents the extrusion of lamellar bodies that are important in barrier maturation and repair. Fewer lamellar bodies means less antimicrobial peptide necessary to combat pathogenic

Table 1 Nutritional agents that stimulate ceramide synthesis

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Effect</th>
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<tbody>
<tr>
<td>Niacinamide</td>
<td>Promotes glucosylerceramide, sphingomyelin, fatty acid, and cholesterol synthesis from in vitro keratinocytes; topical application improved stinging score in patients with sensitive skin; PPAR ligand; up-regulates keratinocyte expression of involucrin and filaggrin</td>
</tr>
<tr>
<td>α-Lipoic acid/ N-acetylcycteine</td>
<td>Strong antioxidants that stimulate ceramide generation in vitro</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>Stimulates PKC and increases the synthesis of ceramide subspecies</td>
</tr>
<tr>
<td>L-Lactic acid</td>
<td>An α-hydroxy acid capable of stimulating lipid synthesis and promoting corneocyte desquamation; may serve as a lipid precursor, donating acetate or providing NADH</td>
</tr>
</tbody>
</table>

NADH, Nicotinamide adenine dinucleotide dehydrogenase; PKC, protein kinase C; PPAR, peroxisome proliferator-activated receptor.

Despite an incomplete pathogenic puzzle, lipid and other nutritional treatments may help facilitate maturation of the permeability barrier and reduce the risk of AD. Nutritional modulation likely begins during gestation, as the risk for AD is encountered as early as in the in utero period. Low levels of arachidonic acid in cord blood have been associated with the risk of dermatitis.46-48 Arachidonic acid is the precursor to series-4 leukotrienes and lipoxins in addition to series-2 prostaglandins (Figure 1). Prostaglandin E2 (PGE2), an arachidonic acid derivative, appears to be involved in the generation of regulatory T cells, which are important in reducing inflammatory responses.39 Trans-fatty acids, derived from the hydrogenation of vegetable oils found in margarine, shortening, and baked goods, inhibit the Δ-5 and Δ-6 desaturase enzymes that are necessary for the conversion of LA and ALA to long-chain products. Concentrations of PUFAs, both cis- and trans- isomers, in cord blood correlate with maternal serum concentrations. An inverse relationship was found between infant trans-fatty acids and arachidonic acid and DHA concentrations in serum.40 Arachidonic acid levels positively correlated with gestational length. Reducing the intake of trans-fatty acids during pregnancy may help reduce the risk of AD by increasing the concentration of arachidonic acid in infant serum. In addition, an increased gestational period likely gives the epidermis more time to mature, decreasing the chances of microbial invasion.

Supplementation with ω-6 in AD

Historically, results of studies of ω-6 supplementation in AD have been conflicting and confusing. The premise behind the use of evening primrose oil, as source of γ-linolenic acid (GLA) in AD comes from studies that showed reduced levels of GLA and dihomo-GLA (DGLA) and higher levels of LA in affected patients, suggesting that a defect in the Δ-6 desaturase enzyme was at work. Many reviews showed a benefit,41 but some were not as promising.42 The most recent meta-analysis on this issue showed that evening primrose oil is effective in a subset of patients with atopic dermatitis and elevated immunoglobulin (Ig) E levels.43

PUFAs, early nutrition, and risk of AD

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organisms like S aureus. Topical steroid application inhibits TLR-3, a signaling molecule important in combating viruses. Genetic defects in the SCPB in AD will make its maturation incomplete.

Applying more physiologic lipids would likely lead to greater healing as lipid mixtures are incorporated into nascent lamellar bodies. Understandably, a mixture of ceramide, cholesterol, and free fatty acids was therefore very effective in the treatment of severe atopic lesions. Whether or not these topical preparations are available, increasing the dietary consumption of beneficial fatty acids like LA and GLA in conjunction with nutritional modalities mentioned in Table 1, while maintaining an acidic environment of the stratum corneum, would likely be of benefit. A 2006 analysis found oral ceramide supplementation improved skin symptoms and allergic responses in atopic children when given at 1.8 g/day for 2 weeks. Wheat germ also contains ceramide precursors, yet the allergic nature of this substrate may limit its utility in some patients.

Immunemodulating roles of ω-3 fatty acids in the epidermis and skin disease

DHA and EPA are not major constituents of the epidermis, which is likely a reflection of insufficient dietary consumption or increased cellular utilization. Unlike LA, which plays a major structural role in the epidermis and SCPB, ω-3 fatty acids appear to play an immune-modulating role. EPA has been shown to reduce the expression of intercellular adhesion molecule-1, reduce T-lymphocyte proliferation, and dampen delayed-type hypersensitivity. A prominent enzyme in the epidermis, 15-lipoxygenase, converts PUFAs into anti-inflammatory mediators that can reduce the production of leukotriene B4, 15-lipoxygenase, converts PUFAs into anti-inflammatory mediators derived from the epidermis. A prominent enzyme in the epidermis, 15-lipoxygenase, converts PUFAs into anti-inflammatory mediators that can reduce the production of leukotriene B4, 15-lipoxygenase, converts PUFAs into anti-inflammatory mediators derived from the epidermis. DHA and EPA have piqued the interest of research oncologists with their protective effect on colorectal cancer and their ability to enhance the effect of chemotherapeutic drugs. DHA and EPA were shown to have a proapoptotic effect on colorectal cancer cells by activation of intrinsic and extrinsic caspase cascades. Many are considering DHA and EPA to be an important adjuvant therapy for many malignancies.

With regard to skin carcinogenesis, ultraviolet radiation is a known carcinogen. One study found that individuals supplemented with 4 g of EPA daily had an increased sunburn threshold, reduced p-53 expression, and fewer strand breaks in peripheral blood leukocytes. Also, in a 20-year observational study of the Inuit, a population known for its vast fish consumption, low rates of melanoma and nonmelanoma skin cancer were reported.

Skin cancer and ω-3 fatty acids

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Systemic lupus erythematosus and ω-3 fatty acids

In systemic lupus erythematosus (SLE), necrosis of cells prevails over apoptosis, and defects in the latter are assumed to be partly pathogenic. Resultant self-derived RNA and DNA immune complexes, derived from necrotic cells, are believed to be taken up by the FcRαI on plasmacytoid dendritic cells and shuttled to endosomal compartments.

Psoriasis and ω-3 fatty acids

Supplementation with fish oil has produced varied results in psoriasis, depending on the method of administration. Improvement has not been seen with topical application or oral supplementation. Improvement was seen when administered intravenously in a randomized, double-blind trial of patients hospitalized with plaque-type psoriasis. Patients were given a combination of 4.2 g of EPA and DHA each vs an ω-6 preparation. Improvements in erythema, scaling, inflammatory infiltrate, and body surface area were observed. It appears that higher doses, and likely longer treatment periods, are necessary for the effects of EPA and DHA to be evident. The intravenous administration of 4.2 g likely equates to double or triple the dose orally. Fish oil supplementation was also shown to reduce the hyperlipidemia and nephrotoxicity associated with retinoid and cyclosporin therapy, respectively.

AD and ω-3 fatty acids

Use of ω-3 fats in pregnancy has been scrutinized, and fish oil supplementation during pregnancy was associated with improvements in clinical severity in AD at 1 year. Early nutrition is highly important for infant development, especially for development of the immune system. In fact, thymic density of breastfed infants is nearly twice that of infants who receive formula. Many studies have shown that breastfeeding has a protective effect on the development of AD. This again is likely a reflection of maternal nutrition, because an increased incidence of AD was found in infants consuming breast milk rich in saturated fat and diminished ω-3 fats. This argues for the importance of DHA and EPA in early life. This recognition has led the U.S. Food and Drug Administration to include the long-chain fatty acids, DHA and arachidonic acid, in infant formulas. Breast milk also contains other factors that protect against AD, including epidermal growth factor, which stimulates keratinocyte growth and migration.

Immune-modulating roles of ω-3 fatty acids in the epidermis and skin disease

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There, these immune complexes activate TLR-7 and TLR-9, leading to the production of interferon (INF)-γ, which is implicated in the pathogenesis of SLE. Selective blocking of TLR-7 and TLR-9 reduced the production of IFN-γ and the further production of autoreactive T cells. Whether DHA and EPA could promote apoptosis of “sunburn cells” is purely speculative at this point. Increasing the sunburn threshold with EPA supplementation may at least be beneficial for patients with SLE. Results of one study showed DHA and EPA levels were reduced in these patients.

**Introduction to the PPARs**

Ligands for the PPARs are emerging as valuable treatments for many diseases, including skin disease. DHA and EPA are natural ligands for these receptors. Synthetic ligands, such as the thiazolidinediones, have been used in psoriasis with success. There are three PPAR isoforms: PPAR-α, PPAR-β/Δ, and PPAR-γ. They are members of the nuclear receptor family that partner with the retinoic acid X receptor to fulfill their functions. Their primary role has been in cardiovascular medicine and endocrinology as lipid regulators and insulin sensitizers. Table 2 summarizes their metabolic functions.

<table>
<thead>
<tr>
<th>PPAR</th>
<th>Function</th>
<th>Synthetic ligands</th>
<th>Natural ligands</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPAR-α</td>
<td>β-oxidation of fatty acids, lipoprotein metabolism, ketogenesis</td>
<td>Fenofibrate, gemfibrozil</td>
<td>DHA and EPA</td>
</tr>
<tr>
<td>PPAR-β/Δ</td>
<td>Adipocyte differentiation and proliferation, cholesterol homeostasis</td>
<td>Thiazolidinediones: rosiglitazone, pioglitazone</td>
<td>DHA and EPA</td>
</tr>
</tbody>
</table>

EPA, Eicosapentaenoic acid; DHA, docosahexaenoic acid.

The anti-inflammatory properties of PPAR-γ make it an interesting candidate for the treatment of inflammatory skin conditions, including psoriasis, AD, acne, and hidradenitis suppurativa. Furthermore, PPAR expression is altered in lesional skin of patients with psoriasis and AD. The anti-inflammatory properties of PPAR-γ have prompted clinical trials to investigate the effectiveness of these medicines in other inflammatory conditions, namely psoriasis, which has been included in the chronic inflammatory spectrum of the metabolic syndrome. A recent double-blind, placebo-controlled trial randomized 41 patients to receive acitretin plus placebo or acitretin plus pioglitazone. After 12 weeks of therapy, a greater reduction in disease was observed in the pioglitazone group.

**Table 3**  Mechanisms of action of epidermal peroxisome proliferator-activated receptors (PPARs)

<table>
<thead>
<tr>
<th>PPAR</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPAR-α</td>
<td>Anti-inflammatory: In a mouse model of irritant contact dermatitis, topical PPAR-α agonists abrogated the intensity of the inflammatory infiltrate and decreased the expression of TNF-α and IL-1, leading to reduced ear swelling. Proapoptotic: In a model of epidermal hyperplasia, PPAR-α application led to enhanced epidermal thinning and apoptosis. Inhibits maturation, migration and T-cell stimulatory properties of Langerhans cells through direct and indirect actions on NF-κB.</td>
</tr>
<tr>
<td>PPAR-β</td>
<td>Anti-apoptotic: activation of PPAR-β protects keratinocytes from cell death. PPAR-β-deficient mice have a hyperplastic epidermis with both exaggerated hyperproliferation and cell death mediated through NF-κB.</td>
</tr>
<tr>
<td>PPAR-γ</td>
<td>In normal mouse skin, topical application of PPAR-γ led to no change in epidermal thickness; whereas, application to hyperproliferative epidermis led to normalization. Proapoptotic</td>
</tr>
</tbody>
</table>

IL, Interleukin; NF-κB, nuclear factor κB; TNF-α, tumor necrosis factor-α.
seen in the treatment group (64.2% vs 51.7%). Although acitretin is known to bind the retinoic acid receptor-α, binding possibly occurs through the retinoic acid X receptor. As stated earlier, PPARs heterodimerize with the retinoic acid X receptor. Therefore, a synergistic effect may be occurring between pioglitazone and acitretin that could potentially reduce the requirement and toxicities of either medication alone. Although systemic administration has been successful, topical application of PPAR activators, including rosiglitazone, have not been shown to be effective in psoriasis.109-111

Acne
Insulin sensitizers, such as the thiazolidinediones and metformin, also have the ability to lower serum androgen levels through the action of PPAR-γ. This makes them intriguing agents for the treatment of acne and hirsutism; however, the adverse side effects of hypoglycemia112 and reports of increased cardiovascular morbidity (pioglitazone) and liver toxicity (troglitazone) may limit their use in acne and psoriasis. All three PPAR isotypes also promote lipogenesis, which could possibly promote acnegenesis.

Atopic dermatitis
The potential application of PPARs in AD is intriguing. Topical PPAR-α therapy shows some promise.113 PPARs have been shown to promote maturation of the SCPB through the following mechanisms:

- stimulating ABCA12 expression, necessary for the uptake of lipids into lamellar bodies
- increasing β-glucocerebrosidase activity
- stimulating lamellar body secretion
- enhancing the synthesis of epidermal fatty acids cholesterol, and sphingomyelin
- increasing markers of terminal differentiation: loricrin, involucrin, trans-glutaminase 1, and profilaggrin114,115

DHA, EPA and other natural PPAR agonists
DHA, EPA, and other natural PPAR agonists may have a more favorable safety profile for use in skin disease. Among the natural PPAR mediators are:

- cis-9, trans-11 conjugated linoleic acid (cLA)
- prostaglandin-J2
- dietary phytochemicals (PPAR-γ receptor agonists): quercetin, luteolin, rosmarinic acid, biochanin A found in red clover
- zingerone found in ginger

These nutrients, including DHA and EPA, are known as "reversible agonists" of PPAR-γ, so higher concentrations are required for receptor activation. Perhaps the improvement in psoriasis observed with intravenous EPA and DHA stated earlier occurs through this mechanism. Prostaglandin-J2 and cLA are produced endogenously. cLA is produced by the actions of gut-derived probiotic bacteria on linoleic acid. The therapeutic effect of probiotics in AD may be a result of cLA production. Roseburia and Lactobacillus crispatus have been shown to produce cLA in vitro. Caution must be taken in purchasing cLA, marketed as a diet aid, because the trans-10, cis-12 isomer that is the predominant form in this preparation induces a stress response in fat cells.

PPARs in wound healing and nonmelanoma skin cancer
PPAR-β activation promotes cell survival by decreasing nuclear and mitochondrial apoptotic pathways.118 This is an important feature for skin wound healing. In fact, PPAR-β is expressed in the keratinocytes of wound edges throughout the duration of the healing process.119 PPAR-β expression has also been shown to be up-regulated in SCC.120 Conversely, PPAR-α and PPAR-γ are antiproliferative and are showing importance in the pathogenesis and treatment of skin cancers. Topical application of PPAR-α reduced human skin inflammation induced from ultraviolet light.121

PPARs in malignant melanoma
PPAR-γ agonists have been shown to inhibit human melanoma proliferation,122 whereas PPAR-α activation inhibits melanoma cell migration.123,124 In parallel, fewer people were diagnosed with melanoma while taking gemfibrozil compared with controls. Some investigators believe that the malignant nature of melanoma cells depends on stimulation of the Wnt/β-catenin pathway and microphthalmia transcription factor pathways.125 Interestingly, ciglitazone, a PPAR-γ ligand, has been shown to cause reductions in both these pathways.125 Therefore, the thiazolidinediones and other PPAR-γ agonists like DHA and EPA pose potential future therapies for melanoma.

TLRs and ω-3 fatty acids
The TLRs are a fairly recently identified group of receptors that are present on many cells, including keratinocytes, monocytes, Langerhans cells, dermal dendritic cells, and intestinal epithelial cells. The TLRs are involved in the first-line recognition of pathogens. They are pattern-recognition receptors that recognize certain pathogen-associated molecular patterns expressed by microbes. TLRs communicate signals of tolerance from recognized commensals or, when danger is sensed, elicit inflammatory responses leading to dendritic cell maturation and activation of adaptive responses. DHA and EPA have been shown, through the consumption of fish oil, to reduce the
proinflammatory signals derived from TLR-2 in human monocytes. In addition, DHA has been shown to inhibit TLR-4, the receptor for lipopolysaccharide.

At least 10 TLRs have been found in humans and can be viewed in 3 categories: lipid/lipopeptide-sensing TLRs (1, 2, 4, and 6), protein-sensing TLRs (5), and nucleic acid-sensing TLRs (3, 7, 8, and 9). The intracellular transmembrane component is homologous to the IL-1 receptor and, in fact, activates a similar intracellular cascade leading to the activation of NF-κB. This leads to production of proinflammatory cytokines and antimicrobial peptides, and up-regulation of chemokines, adhesion molecules, and co-stimulatory molecules.

Briefly, TLR-1, -2, and -6 can homodimerize or heterodimerize with each other; they are lipid/lipoprotein receptors, bind peptidoglycan, and recognize microbes such as S epidermitis, S aureus, Mycoplasma, and Mycobacteria. The role of TLR-2 may be to aid in establishing tolerance to nonpathogenic bacteria, because signaling through TLR-2 alone leads to the induction of IL-10 and reduced cell-mediated immunity. Heterodimerization with TLR-1 leads to increased cell-mediated immunity.

**EPA and DHA, TLR-2 and TLR-4, and skin disease**

EPA and DHA may help reduce inflammatory responses in AD and psoriasis by modulation of TLR-2 and TLR-4.

**AD and psoriasis**

Patients with AD are chronically colonized by S aureus, a known stimulator of TLR-2. Recent studies have identified a group of severe atopics with polymorphisms in the TLR-2 gene. Increased expression of TLR-2 has been found in lesional keratinocytes in patients with psoriasis. In addition, antikeratin 16 antibodies that are increased in patients with psoriasis were found to increase the messenger RNA expression of TLR-2 and TLR-4.

**Acne vulgaris**

In acne, sebocytes are known to express TLR-2 and TLR-4 constitutively. Propionibacterium acnes can activate TLR-2 on macrophages, leading to IL-12 and IL-8 production and neutrophil recruitment. Inflammation can be perpetuated through TLR-2 on macrophages, leading to IL-12 and IL-8 production and neutrophil recruitment. Inflammation can be perpetuated by TLR-2 on macrophages, leading to IL-12 and IL-8 production and neutrophil recruitment. Inflammation can be perpetuated by TLR-2 on macrophages, leading to IL-12 and IL-8 production and neutrophil recruitment. Inflammation can be perpetuated by TLR-2 on macrophages, leading to IL-12 and IL-8 production and neutrophil recruitment.

**Conclusions**

The mechanisms of the nutritional deficiency dermatosis originally recognized by Burr and Burr are becoming more fully understood as the diverse and elaborate roles of the PUFAs are elucidated. Furthermore, PUFAs are proving to be essential to healthy skin and aid in the healing of diseased skin.

A fatty acid profile can help identify patients with suboptimal fatty acid concentrations. Absolute fatty acid concentrations, ω-6/ω-3 ratios, and mead acid levels—a marker of essential fatty acid deficiency—can be evaluated from this parameter. Western diets and disease make us more dependent on obtaining GLA, arachidonic acid, EPA, and DHA from the diet. Consumption of LA in the form of sunflower seeds, poppy seeds, and wheat germ, as well as ceramide supplements, can provide the epidermis with precursors for the synthesis of ceramides that are important in the formation of the extracellular lipid matrix. The epidermis depends on lipids for maturation and repair, because perturbations in the permeability barrier lead to the up-regulation of genes important in fatty acid uptake, the mechanisms of which are more selective for LA. In addition, physiologic lipids such as ceramides and free fatty acids applied topically do not impede maturation of the epidermis as occlusive petrolatum does.

Maintaining an acidic environment by limiting bleach baths and applying topical lactate and ascorbic acid (vitamin C) appears to promote natural ceramide synthesis. Niacinamide, α-lipoic acid and N-acetylcysteine are other nutrients that stimulate ceramide generation. Dietary evening primrose oil, a form of GLA (ω-6), appears to be effective in the subset of AD patients with an allergic phenotype and high IgE levels. Finally, reducing the dietary intake of trans-fatty acids and saturated fats during pregnancy is associated with, respectively, lower risk of AD and a less severe phenotype.

Increasing the intake of green leafy vegetables, nuts, seeds, and cold-water fish over time can improve the concentration of ω-3 fatty acids in cellular membranes. The hydroxylated variants of DHA, EPA, and DGLA—17-hydroxyeicosahexanoic acid, 15-hydroxyeicosahexanoic acid, and 15-hydroxyeicosatrienoic acid—respectively, can temper inflammatory mediators such as leukotriene B4 and improve psoriatic lesions. Studies have shown that high doses of fish oil rich in EPA and DHA improved psoriasis in hospitalized patients when administered intravenously and reduced acitretin-associated hyperlipidemia and cyclosporin-induced nephrotoxicity.

DHA and EPA are proapoptotic and may soon be used as an adjunct treatment for many malignancies due to their ability to activate caspase cascades, induce apoptosis, and enhance the effects of chemotherapeutic medicines. PUFAs may also be a useful addition for the prevention of skin carcinogenesis and alleviate photosensitive eruptions by increasing the sunburn threshold and reducing damage to DNA.
DHA and EPA are not found in great supply in the epidermis, which may reflect insufficient dietary intake or increased cellular utilization, because these fatty acids are important anti-inflammatory and antiproliferative cellular messengers activating PPARs and TLRs. PPAR-γ ligands are anti-inflammatory. High-dose essential fat therapy may be a safer alternative to pioglitazone, a PPAR-γ ligand, in the treatment of psoriasis. Coadministration of PUFAs with acitretin in psoriasis patients may reduce adverse effects and augment the clinical outcome.\(^\text{109}\)

Topical PPAR-α is showing promise in AD with its ability to facilitate healing of the permeability barrier.\(^\text{114}\) PPARs are also antiproliferative and antimetastatic and may control specific pathways involved in melanoma.\(^\text{124-126}\) Finally, EPA and DHA may help control inflammation in acne and psoriasis through TLR-2 and TLR-4 binding.\(^\text{131}\)

Linoleic acid, \(\gamma\)-linolenic acid, eicosapentaenoic acid, and docosahexanoic acid are vital to optimum wellness and healthy skin. Poor maternal nutrition, infancy, consuming a Western diet, age, and diabetic states are conditions where increased dietary intake is required and nutritional supplementation is essential to restore the balance of \(\alpha\)-6:0-3 fatty acids. As we have discussed, these fatty acids and their synthetic derivatives serve important and diverse roles in the structural maintenance and immunologic balance of the epidermis and may aid in the healing of many dermatoses by the following mechanisms:

- maintenance of the stratum corneum permeability barrier
- maturation and differentiation of the stratum corneum
- formation and secretion of lamellar bodies
- inhibition of proinflammatory eicosanoids
- elevation of the sunburn threshold
- inhibition of proinflammatory cytokines, including TNF-\(\alpha\), IFN-\(\gamma\), and IL-12
- inhibition of lipoxygenase
- promotion of wound healing
- promotion of apoptosis in malignant cells including melanoma
- modulation of PPARs
- inhibition of proinflammatory signals mediated through TLRs

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