Clinics in Dermatology (2010) **28**, 440–451

ELSEVIER

Clinics in Dermatology

Healing fats of the skin: the structural and immunologic roles of the ω-6 and ω-3 fatty acids

Meagen M. McCusker, MD, Jane M. Grant-Kels, MD*

Department of Dermatology University of Connecticut Health Center, 263 Farmington Avenue, MC 6230, Farmington, CT 06030, USA

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 lipoxygenase, 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.

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

* Corresponding author. Tel.: +1 860 670 3474.
E-mail address: grant@uchc.edu (J.M. Grant-Kels).

0738-081X/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.clindermatol.2010.03.020

notable in atopic dermatitis. Derivatives of α-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 (20:3ω-9) 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 (18:1ω-9) 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 envelop, and dense keratin fibrils aggregated by filaggrin. 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 envelop proteins loricrin, involucrin, and trichohyalin by *trans*-glutaminase. The extracellular lipid matrix coats the cornified envelop proteins, forming a strong, water-impervious lamella.

Defective SCPB results when mutations occur in the proteins and enzymes that are important in this complex process[11,12] 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-hydroxyceramide, an important anchoring lipid connecting the extracellular lipid matrix to the

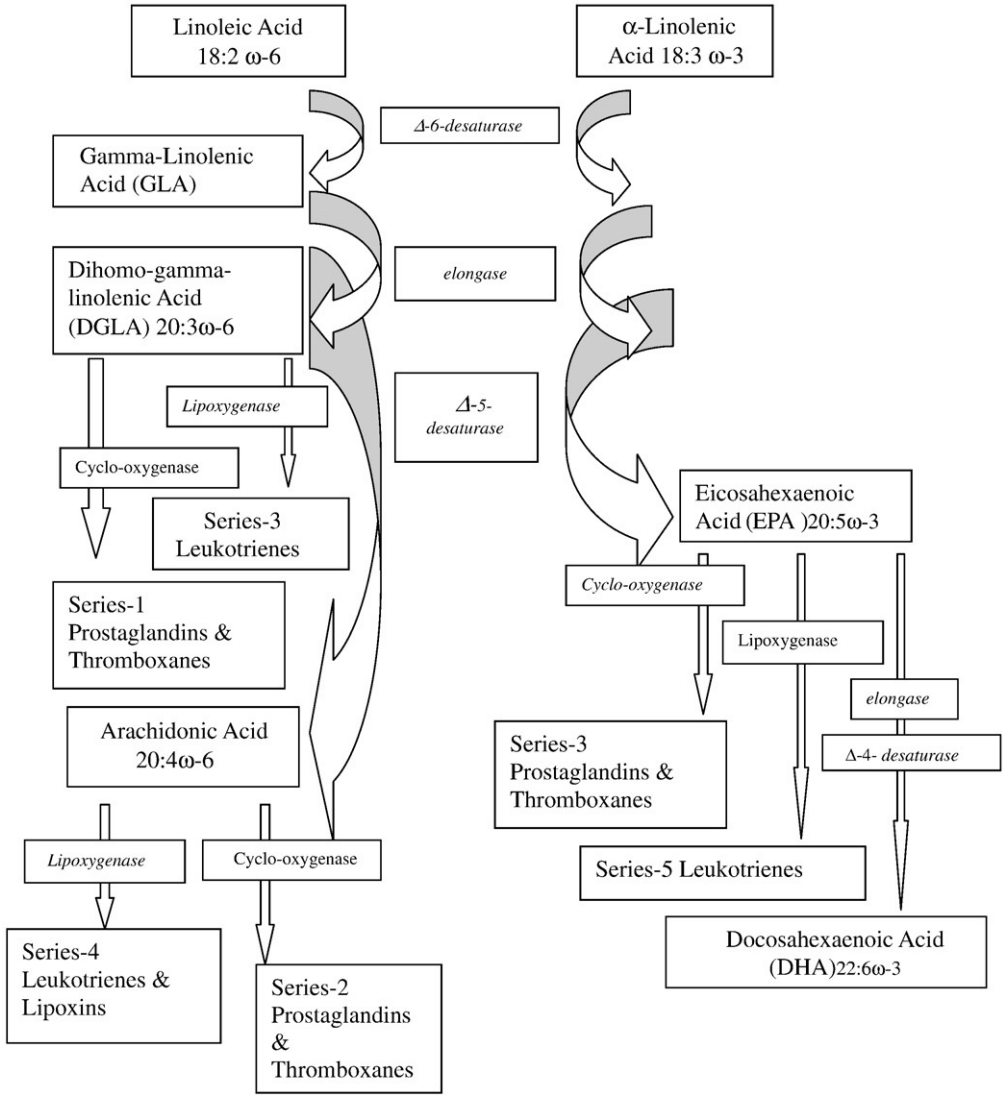

Fig. 1 Fatty acid derivatives and lipid mediators from linoleic acid and α-linolenic acid.

cornified envelop. Therefore, PUFA insufficiency results in increased transepidermal water loss.[21] Proliferative keratins (K6 and K16) and inflammation-associated keratins (K17) are also induced as a result of PUFA deficiency.[22] These findings highlight the necessity of dietary fatty acids, especially ω-6 fats, in epidermal homeostasis and the SCPB.[23]

SCPB and healthy skin

An acid environment is critical for the functioning of acid sphingomyelinase and β-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 [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.[25] Use of statins in elderly patients may exacerbate xerosis, because topical lovastatin resulted in barrier irregularities and hyperproliferation of the epidermis.[26] Other nutritional agents that stimulate ceramide synthesis and promote a healthy permeability barrier are listed in Table 1.[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.[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

Table 1 Nutritional agents that stimulate ceramide synthesis

Nutrient	Effect
Niacinamide	Promotes glucosylceramide, sphingomyelin, fatty acid, and cholesterol synthesis from in vitro keratinocytes[27]; topical application improved stinging score in patients with sensitive skin[28]; PPAR ligand; up-regulates keratinocyte expression of involucrin and filaggrin[29]
α-Lipoic acid/ *N*-acetylcysteine	Strong antioxidants that stimulate ceramide generation in vitro[30]
Ascorbic acid	Stimulates PKC and increases the synthesis of ceramide subspecies[31]
L-Lactic acid	An α-hydroxy acid capable of stimulating lipid synthesis and promoting corneocyte desquamation; may serve as a lipid precursor, donating acetate or providing NADH[32]

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

AD have genetic defects in filaggrin. With the complexity and orchestration of precursors and enzymes necessary to complete an effective permeability barrier, other errors are likely to surface. In addition, although an incompetent barrier in AD predisposes patients to continual antigen invasion and inflammation, patients with inherited filaggrin defects in ichthyosis vulgaris do not maintain the same degree of inflammation,[34] arguing for defects in immunity in AD as well. Interleukin (IL)-4 and IL-13, known pathogenic cytokines in AD, have been shown to reduce filaggrin gene expression in cultured keratinocytes.[35]

PUFAs, early nutrition, and risk of AD

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.[36-38] Arachidonic acid is the precursor to series-4 leukotrienes and lipoxins in addition to series-2 prostaglandins (Figure 1). Prostaglandin E_2 (PGE_2), 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 deduced 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 SCPB 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

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.[56] Understandably, a mixture of ceramide, cholesterol, and free fatty acids was therefore very effective in the treatment of severe atopic lesions.[57] 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.[58] Wheat germ also contains ceramide precursors, yet the allergic nature of this substrate may limit its utility in some patients.

Immune-modulating 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,[59] reduce T-lymphocyte proliferation, and dampen delayed-type hypersensitivity.[60] Diets supplemented with fish oil can lead to altered phospholipid profiles in the epidermis.[61,62] A prominent enzyme in the epidermis, 15-lipoxygenase, converts PUFAs into anti-inflammatory mediators that can reduce the production of leukotriene B4, a potent inflammatory and antimicrobial mediator derived from the proinflammatory enzyme 5-lipoxygenase on arachidonic acid. Elevated leukotriene B4 has been found in lesions of guttate psoriasis.[63] Zileuton, a known inhibitor of leukotriene B4, has been shown to improve psoriasis[64] and pruritus in Sjögren-Larsson syndrome.

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.[65] 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.[66] Many studies have shown that breastfeeding has a protective effect on the development of AD.[67,68] 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.[69] 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.[70]

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[71] or oral supplementation.[72] Improvement was seen when administered intravenously in a randomized, double-blind trial of patients hospitalized with plaque-type psoriasis.[73] 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.[74,75]

Skin cancer and ω-3 fatty acids

DHA and EPA have piqued the interest of research oncologists with their protective effect on colorectal cancer[76] and their ability to enhance the effect of chemotherapeutic drugs.[77] 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.[77]

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.[78] 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.[79]

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 FcεRII on plasmacytoid dendritic cells and shuttled to endosomal compartments.[80,81]

Table 2 Metabolic functions of peroxisome proliferator-activated receptor *(PPAR)*

PPAR	Function	Synthetic ligands	Natural ligands
PPAR-α	β-oxidation of fatty acids,[86] lipoprotein metabolism,[87,88] ketogenesis[89]	Fenofibrate, gemfibrozil	DHA and EPA
PPAR-β/Δ	Adipocyte differentiation and proliferation, cholesterol homeostasis[90,91]		DHA and EPA
PPAR-γ	Cell growth and differentiation; glucose and lipid homeostasis[92]	Thiazolidinediones: rosiglitazone, troglitazone, and pioglitazone	DHA and EPA

EPA, Eicosapentaenoic acid; *DHA,* docosahexaenoic acid.

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.[82] Selective blocking of TLR-7 and TLR-9 reduced the production of IFN-γ and the further production of autoreactive T cells.[83] 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.[84]

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.[85] 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.[86-92]

PPAR-γ is particularly notable because it has strong anti-inflammatory properties, including:

- inhibiting tumor necrosis factor-α (TNF-α) generation from adipocytes[93]
- inhibiting macrophage-induced IFN-γ production[94,95]
- inhibiting the activity of lipoxygenase[96] and
- decreasing the secretion of IL-12 from dendritic cells[97,98]

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.[99,100]

PPAR expression in the skin

Adult keratinocytes, Langerhans cells, and melanocytes express all PPAR isotypes.[101-103] Mechanisms of epidermal PPAR actions have been elucidated in experimental models of skin disease, which are summarized in Table 3.[104-108]

PPARs and skin disease

Psoriasis

The anti-inflammatory properties of PPARs 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.[85] After 12 weeks of therapy, a greater reduction in disease was

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

PPAR	Action
PPAR-α	• 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[104] • Proapoptotic: In a model of epidermal hyperplasia, PPAR-α application led to enhanced epidermal thinning and apoptosis[105] • Inhibits maturation, migration and T-cell stimulatory properties of Langerhans cells through direct and indirect actions on NF-κB[106]
PPAR-β	• Anti-apoptotic: activation of PPAR-β protects keratinocytes from cell death[106] • PPAR-β-deficient mice have a hyperplastic epidermis with both exaggerated hyperproliferation and cell death[107] mediated through NF-κB.
PPAR-γ	• In normal mouse skin, topical application of PPAR-γ led to no change in epidermal thickness; whereas, application to hyperproliferative epidermis led to normalization[108] • Proapoptotic

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 hypoglycemia[112] 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[14]
- 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 profilaggrin[114,115]

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[116]:

- *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.[117]

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.[126] In addition, DHA has been shown to inhibit TLR-4, the receptor for lipopolysaccharide.[83]

At least 10 TLRs have been found in humans[127] 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).[83] The intracellular transmembrane component is homologous to the IL-1 receptor[128] 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.[129]

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.[130] Increased expression of TLR-2 has been found in lesional keratinocytes in patients with psoriasis.[83] In addition, antikeratin 16 antibodies that are increased in patients with psoriasis[131] were found to increase the messenger RNA expression of TLR-2 and TLR-4.[132]

Acne vulgaris

In acne, sebocytes are known to express TLR-2 and TLR-4 constitutively.[133] *Propionibacterium acnes* can activate TLR-2 on macrophages, leading to IL-12 and IL-8 production and neutrophil recruitment. Inflammation can be perpetuated by keratinocytes by *P acnes* induction of TLR-4 (not typically expressed on keratinocytes) and TLR-2 activation. EPA and DHA may therefore be helpful in modulating this inflammation. While DHA and EPA may be functioning to control inflammation, other antimicrobial fatty acids at the skin surface are trying to eliminate *P acnes.* Lauric acid is an antimicrobial fatty acid found in coconut oil and breast milk. It is also produced by sebaceous glands and is a stimulator of TLR-2. This fat, when applied topically, reduced the numbers of *P acnes* colonies at the epidermal surface and was nontoxic to sebocytes.[134] Oral supplementation with DHA and EPA could then serve as a perfect adjunct to this potential antiacne drug by modulating inflammation and irritation.

Conclusions

The mechanisms of the nutritional deficiency dermatosis originally recognized by Burr and Burr[1,2] 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.[3] Western diets and disease make us more dependent on obtaining GLA, arachidonic acid, EPA, and DHA from the diet.[7] 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,[46-54] the mechanisms of which are more selective for LA.[13-16] In addition, physiologic lipids such as ceramides and free fatty acids applied topically do not impede maturation of the epidermis as occlusive petrolatum does.[56]

Maintaining an acidic environment by limiting bleach baths and applying topical lactate and ascorbic acid (vitamin C) appears to promote natural ceramide synthesis.[32,31] Niacinamide, α-lipoic acid and *N*-acetylcysteine are other nutrients that stimulate ceramide generation.[27-30] 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.[43] 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.[40,65]

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.[63,64] Studies have shown that high doses of fish oil rich in EPA and DHA improved psoriasis in hospitalized patients when administered intravenously[73] and reduced acitretin-associated hyperlipidemia and cyclosporin-induced nephrotoxicity.[75]

DHA and EPA are proapoptotic and may soon be used as an adjuvant treatment for many malignancies due to their ability to activate caspase cascades, induce apoptosis, and enhance the effects of chemotherapeutic medicines.[76,77] 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.[78]

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.[109]

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

Linoleic acid, γ-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 ω-6:ω-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-α, IFN-γ, 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

References

1. Burr GO, Burr MM. A new deficiency disease produced by the rigid exclusion of fat from the diet. J Biol Chem 1929;82:345-67.
2. Burr GO, Burr MM. On the nature and role of the fatty acids essential in nutrition. J Biol Chem 1930;86:587-621.
3. Cunnane SC. Problems with essential fatty acids: time for a new paradigm? Prog Lipid Res 2003;42:544-68.
4. Larsson SC, Kumlin M, Ingelman-Sundberg M, Wolk A. Dietary long-chain n-3 fatty acids for the prevention of cancer: a review of potential mechanisms. Am J Clin Nutr 2004;79:935-45.
5. Das UNA. Perinatal strategy for preventing adult diseases: the role of long-chain polyunsaturated fatty aids. Boston: Kluwer; 2002.
6. Ollis TE, Meyer BJ, Howe PR. Australian food sources and intakes of omega-6 and omega-3 polyunsaturated fatty acids. Ann Nutr Metab 1999;43:346-55.
7. Das UN. Essential fatty acids: biochemistry, physiology and pathology. Biotech J 2006;1:420-39.
8. Jump DB. The biochemistry of n-3 polyunsaturated fatty acids. J Biol Chem 2002;277:8755-8.
9. Wertz PW. Biochemistry of human stratum corneum lipids. In: Elias PM, Feingold KR, editors. Skin barrier. New York: Taylor & Francis; 2006. p. 33-42.
10. Elias P, Feingold K, Fartasch M. Epidermal lamellar body as a multifunctional secretory organelle. In: Elias PM, Feingold KR, editors. Skin barrier. New York: Taylor & Francis; 2006. p. 261-72.
11. Akiyama M, Sugiyama-Nakagiri Y, Sakai K, et al. Mutations in lipid transporter ABCA12 in harlequin ichthyosis and functional recovery by corrective gene transfer. J Clin Invest 2005;115:1777-84.
12. Hovnanian A. Harlequin ichthyosis unmasked: a defect of lipid transport. J Clin Invest 2005;115:1708-10.
13. Menon GK, Feingold KR, Moser AH, Brown BE, Elias PM. De novo sterologenesis in the skin, II. Regulation by cutaneous barrier requirements. J Lipid Res 1985;26:418-27.
14. Grubauer G, Feingold KR, Elias PM. Relationship of epidermal lipogenesis to cutaneous barrier function. J Lipid Res 1987;28:746-52.
15. Bhattacharyya AK, Connor WE, Spector AA. Excretion of sterols from normal and hypercholesterolemic humans. Implications for sterol balance studies. J Clin Invest 1972;51:2060-70.
16. Nikkari T, Schreibman PH, Ahrens EH. Isotope kinetics of human skin cholesterol secretion. J Exp Med 1975;141:620-34.
17. Elias PM, Brown BE. The mammalian cutaneous permeability barrier: defective barrier function in essential fatty acid deficiency correlates with abnormal intercellular lipid deposition. Lab Invest 1978;39:574-83.
18. Hansen HS, Jensen B. Essential function of linoleic acid esterified in acylglycosylceramide and acylceramide in maintaining the epidermal water permeability barrier. Evidence from feeding studies with oleate, linoleate, arachidonate, columbinate and alpha-linoleate. Biochim Biophys Acta 1985;834:357-63.
19. Melton JL, Wertz PW, Swartzendruber DC, Downing DT. Effects of essential fatty acid deficiency on epidermal O-acylsphingolipids and transepidermal water loss in young pigs. Biochim Biophys Acta 1987;921:191-7.
20. Wertz PW, Cho ES, Downing DT. Effect of essential fatty acid deficiency on the epidermal sphingolipids of the rat. Biochim Biophys Acta 1983;753:350-5.
21. Meguro S, Arai Y, Masukawa Y, Uie K, Tokimitsu I. Relationship between covalently bound ceramides and transepidermal water loss (TEWL). Arch Derm Res 2000;292:463-8.
22. Ekanayake-Mudiyanselage S, Aschauer H, Schmook FP, Jensen JM, Meingassner JG, Proksch E. Expression of epidermal keratins and the cornified envelop protein involucrin is influenced by permeability barrier disruption. J Invest Dermatol 1998;111:517-23.
23. Schurer NY, Stremmel W, Grundmann JU, et al. Evidence for a novel keratinocyte fatty acid uptake mechanism with preference for linoleic acid: comparison of oleic acid and linoleic acid uptake by cultured human keratinocytes, fibroblasts and a human hepatoma cell line. Biochin Biophys Acta 1994;1211:51-60.
24. Elias PM, Hatano Y, Williams ML. Basis for the barrier abnormality in atopic dermatitis: outside-inside-outside pathogenic mechanisms. J Allergy Clin Immunol 2008;121:1337-43.
25. Rawlings AV. Trends in stratum corneum research and the management of dry skin conditions. Int J Cosmet Sci 2003;25:63-95.
26. Proksch E, Feingold KR, Elias PM. Epidermal HMG CoA reductase activity in essential fatty acid deficiency: barrier requirements rather than eicosanoid generation regulate cholesterol synthesis. J Invest Dermatol 1992;99:216-20.
27. Tanno O, Ota Y, Hikima R, Matsumoto M, Ota M, Inoue S. An increase in endogenous epidermal lipids improves skin barrier function. 20th IFSCC International Congress; 2000. p. 347-58.

28. Ertel KD, Berge CA, Mercurio MG, et al. New facial moisturizer technology increase exfoliation without compromising barrier function. Proceedings of the 58th Annual Meeting of the American Academy of Dermatology, San Francisco, CA; 2000.
29. Oblong JE, Bissett DL, Ritter JL, Kurtz KK, Schnicker MS. Niacinamide stimulates collagen synthesis from human dermal fibroblasts and differentiation markers in normal human epidermal keratinocytes: potential of niacinamide to normalize aged skin cells to correct homeostatic balance. Proceedings of the 59th Annual Meeting of the American Academy of Dermatology, Washington, DC; 2001.
30. Zhang K, Kosturko K, Rawlings AV. The effect of thiols on epidermal lipid biosynthesis. Annual Meeting of The Society For Investigative Dermatology. J Invest Dermatol 1995;104:687.
31. Uchida Y, Behne M, Quice D, et al. Vitamin C stimulates sphingolipid production and markers of barrier formation in submerged human keratinocyte cultures. J Invest Dermatol 2001;117:1307-13.
32. Rawlings AV, Davies A, Carlomusto M, et al. Effect of lactic acid isomers on keratinocyte ceramide synthesis, stratum corneum lipid levels and stratum corneum barrier function. Arch Dermatol Res 1996;288:383-90.
33. Palmer CN, Irvine AD, Terron-Kwiatkowski A, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nat Genet 2006;38: 441-6.
34. Sandilands A, Terron-Kwiatkowski A, Hull PR, et al. Comprehensive analysis of the gene encoding filaggrin uncovers prevalent and rare mutations in ichthyosis vulgaris and atopic eczema. Nat Genet 2007;39:650-4.
35. Howell MD, Kim BE, Gao P, et al. Cytokine modulation of atopic dermatitis filaggrin skin expression. J Allergy Clin Immunol 2009;124 (3 suppl 2):R7-R12.
36. Strannegard I, Svennerholm L, Strannegard O. Essential fatty acids in serum lecithin of children with atopic dermatitis and in umbilical cord serum of infants with high or low IgE levels. Int Arch Allergy Appl Immunol 1987;82:422-3.
37. Galli E, Picardo M, Chini L, et al. Analysis of polyunsaturated fatty acids in newborn sera: a screening tool for atopic disease? Br J Dermatol 1994;130:752-6.
38. Beck M, Zelczak G, Lentze MJ. Abnormal fatty acid composition in umbilical cord blood of infants at high risk of atopic disease. Paediatr 2000;89:279-84.
39. Laitinen K, Hoppu U, Hamalainen M, Linderborg K, Moilanen E, Isolaurie E. Breast milk fatty acids may link innate and adaptive immune regulation: analysis of soluble CD14, prostaglandin E2, and fatty acids. Pediatr Res 2006;59:723-7.
40. Elias SL, Innis SM. Infant plasma trans, n-6, and n-3 fatty acids and conjugated linoleic acids are related to maternal plasma fatty acids, length of gestation, and birth weight and length. Am J Clin Nutr 2001;73:807-14.
41. Horrobin DF. Essential fatty acid metabolism and its modification in atopic eczema. Am J Clin Nutr 2000;71(1suppl):367S-72S.
42. Biagi PL, Bordoni A, Masi M, et al. The effect of gamma-linolenic acid on clinical status, red cell fatty acid composition and membrane microviscosity in infants with atopic dermatitis. Drugs Exp Clin Res 1994;14:285-90.
43. Morse NL, Clough PM. A meta-analysis of randomized, placebo-controlled clinical trials of efamol evening primrose oil in atopic eczema. Where do we go from here in light of more recent discoveries. Curr Pharma Biotech 2006;7:503-24.
44. Okino N, Tani M, Imayama S, Ito M. Purification and characterization of a novel ceramidase from Pseudomonas aeruginosa. J Biol Chem 1998;273:14368-73.
45. Ohnishi Y, Okino N, Ito M, Imayama S. Ceramidase activity in bacterial skin flora as a possible cause of ceramidase deficiency in atopic dermatitis. Clin Diagn Lab Immun 1999;6:101-4.
46. Jackson SM, Wood LC, Lauer S, et al. Effect of cutaneous permeability barrier on HMG CoA reductase, LDL receptor, and apolipoprotein E mRNA levels in the epidermis of hairless mice. J Lipid Res 1992;33:1307-14.
47. Proksch E, Elias PM, Reingold KR. Regulation of 3-hydroxy-3-methylglutaryl-coenzyme A reductase activity in murine epidermis. Modulation of enzyme content and activation state by barrier requirements. J Clin Invest 1990;85:874-82.
48. Harris IR, Farrell AM, Grunfeld C, Holleran WM, Elias PM, Feingold KR. Permeability barrier disruption coordinately regulates mRNA levels for key enzymes of cholesterol, fatty acid, and ceramide synthesis in the epidermis. J Invest Dermatol 1997;109:783-7.
49. Ottey KA, Wood LC, Grunfield C, Elias PM, Feingold KR. Cutaneous permeability barrier disruption increases fatty acid synthetic enzyme activity in the epidermis of hairless mice. J Invest Dermatol 1995;104: 401-4.
50. Feingold KR. The role of epidermal lipids in cutaneous permeability barrier homeostasis. J Lipid Res 2007;48:2531-46.
51. Bleck B, Hohoff C, Binas B, et al. Cloning and chromosomal localisation of the murine epidermal-type fatty acid binding protein gene (Fabpe). Gene 1998;215:123-30.
52. Madsen P, Rasmussen HH, Leffers H, Honore B, Celis JE. Molecular cloning and expression of a novel keratinocyte protein (psoriasis-associated faty acid-binding protein [PA-FABP] that is highly upregulated in psoriatic skin and that shares similarity to fatty acid-binding proteins. J Invest Dermatol 1992;99:299-305.
53. Siegenthaler G, Hotz R, Chatellard-Gruaz D, Didierjean L, Hellman U, Saurat JH. Purification and characterization of the human epidermal fatty acid-binding protein: localization during epidermal cell differentiation in vivo and in vitro. Biochem J 1994;302:363-71.
54. Siegenthaler G, Hotz R, Chatellard-Gruaz D, Jaconi S, Saurat JH. Characterization and expression of a novel fatty acid-binding protein: the epidermal type (E-FABP). Biochem Biophys Res Commun 1993;190:482-7.
55. Di Marzio L, Centi C, Cinque B, et al. Effect of the lactic acid bacterium *Streptococcus thermophilus* on the stratum corneum ceramide levels and signs and symptoms of atopic dermatitis patients. Exp Dermatol 2003;12:615-20.
56. Mao-Qiang M, Brown BE, Wu-Pong S, Feingold KR, Elias PM. Exogenous nonphysiological vs physiological lipids. Divergent mechanisms for correction of permeability barrier dysfunction. Arch Dermatol 1995;131:809-16.
57. Sugarman J, Parish LJ. A topical lipid-based barrier repair formulation (EpiCeram™ cream) is high effective monotherapy for moderate-to-severe pediatric atopic dermatitis. J Invest Dermatol 2000;115:414-20.
58. Kimata H. Improvement of atopic dermatitis and reduction of skin allergic responses by oral intake of konjac ceramide. Pediatr Dermatol 2006;23:386-9.
59. Hughes DA, Pinder AC, Piper Z, Johnson IT, Lund EK. Fish oil supplementation inhibits the expression of major histocompatibility complex class II molecules and adhesion molecules on human monocytes. Am J Clin Nutr 1996;63:267-72.
60. Kelley DS, Branch LB, Love JE, Taylor PC, Rivera YM, Lacono JM. Dietary alpha-linoleic acid and immunocompetence in humans. Am J Clin Nutr 1991;53:40-6.
61. Miller CC, Ziboh VA, Wong T, Fletcher MP. Dietary supplementation with n-3 and n-6 enriched oils influences in vivo levels of epidermal lipoxygenase products. J Nutr 1990;120:36-44.
62. Miller CC, Tang W, Ziboh VA, Fletcher MP. Dietary supplementation with ethyl ester concentrations of fish oil (n-3) and borage oil (n-6) polyunsaturated fatty acids induces epidermal generation of local putative antiinflammatory metabolites. J Invest Dermatol 1991;96: 98-103.
63. Fogh K, Herlin T, Kragballe K. Eicosanoids in acute and chronic psoriatic lesions: Leukotriene B4, but not 12-hydroxy-eicosatetraenoic acid, is present in biologically active amounts in acute guttate lesions. J Invest Dermatol 1989;92:837-41.
64. Black AK, Camp RD, Mallet AI, Cunningham FM, Hofbauer M, Greaves MW. Pharmacologic and clinical effects of lonapalene (RS

43179), a 5-lipoxygenase inhibitor, in psoriasis. J Invest Dermatol 1990;95:50-4.
65. Denburg J, Hatfield H, Cyr M, et al. Fish oil supplementation in pregnancy modifies neonatal progenitors at birth in infants at risk of atopy. Pediatr Res 2005;57:276-81.
66. Newburg DS, Walker WA. Protection of the neonate by the innate immune system of developing gut and of human milk. Pediatr Res 2007;61:2-8.
67. Bergmann RL, Diepgen TL, Kuss O, et al. MAS-study group. Breastfeeding duration is a risk factor for atopic eczema. Clin Exp Allergy 2002;32:205-9.
68. Gdalevich M, Mimouni D, David M, Mimouni M. Breastfeeding and the onset of atopic dermatitis in childhood: A systematic review and meta-analysis of prospective studies. J Am Acad Dermatol 2001;45: 520-7.
69. Hoppu U, Rinne M, Lampi A, Isolaurie E. Breast milk fatty acid composition is associated with development of atopic dermatitis in the infant. J Pediatr Gastroenterol Nutr 2005;41:335-8.
70. Gibbs S, Pinto ANS, Murli S, Huber M, Hohl D, Ponec M. Epidermal growth factor and keratinocyte growth factor differentially regulate epidermal migration, growth and differentiation. Wound Rep Regen 2009;8:192-203.
71. Henniecke-von Zepelin HH, Mrowietz U, Farber L, et al. Highly purified omega-3-polyunsaturated fatty acids for topical treatment of psoriasis. Results of a double-blind, placebo-controlled multicentre study. Br J Dermatol 1993;129:713-7.
72. Soyland E, Funk J, Rajka G, et al. Dietary supplementation with very long-chain n-3 fatty acids in patients with atopic dermatitis: a double-blind, multicentre study. Br J Dermatol 1994;130:757-64.
73. Mayser P, Mrowietz U, Arenberger P, et al. Omega-3 fatty acid-bsed lipid infusion in patients with chronic plaque psoriasis: Results of a double-blind, randomized, placebo-controlled, multicenter trial. J Am Acad Dermatol 1998;38:539-47.
74. Simopoulos AP. Omega-3 fatty acids in inflammation and autoimmune diseases. J Amer Coll Nutr 2002;21:495-505.
75. Allen BR. Fish oil in combination with other therapies in the treatment of psoriasis. World Rev Nutr Diet 2001;66:436-45.
76. Giros A, Grzybowski M, Sohn VR, et al. Regulation of colorectal cancer cell apoptosis by the n- polyunsaturated fatty acids docosahexaenoic and eicosapentaenoic. Cancer Prev Res 2009;2:732-42.
77. Biondo PD, Brindley DN, Sawyer MB, Field CJ. The potential for treatment with dietary long-chain polyunsaturated n-3 fatty acids during chemotherapy. J Nutr Biochem 2008;19:787-96.
78. Rhodes LE, Shahbakhti H, Azurdia RM, et al. Effect of eicosapentanoic acid an omega-3 polyunsaturated fatty acid, on UVR-related skin cancer risk in humans: An assessment of early genotoxic markers. Carcinogenesis 2003;24:919-25.
79. Miller AB, Gaudette LA. Cancers of skin, bone, connective tissue, brain, eye, thyroid and other specified and unspecified sites in Inuit. Acta Oncol 1996;35:607-16.
80. Bave U, Magnusson M, Eloranta ML, Perers A, Alm GV, Ronnblom L. Fc gamma RIIa is expressed on natural IFN-alpha-producing cells (plasmacytoid dendritic cells) and is required for the IFN-alpha production induced by apoptotic cells combined with lupus IgG. J Immunol 2003;171:3296-302.
81. Means TK, Latz E, Hayashi F, Murali MR, Golenbock DT, Luster AD. Human lupus autoantibody–DNA complexes activated DCs through cooperation of CD32 and TLR9. J Clin Invest 2005;115:407-17.
82. von Wussow P, Jakschies D, Hochkeppel H, Horisberger M, Hartung K, Deicher H. MX homologous protein in mononuclear cells from patients with systemic lupus erythematosus. Arthritis Rheum 1989;32: 914-8.
83. Barrat FJ, Coffman RL. Development of TLR inhibitors for the treatment of autoimmune diseases. Immunol Rev 2008;223:271-83.
84. Mohan IK, Das UN. Oxidant stress, anti-oxidants and essential fatty acids in systemic lupus erythematosus. Prostaglandins Leukot Essent Fatty Acids 1997;56:193-8.
85. Mittal R, Malhotra S, Pandhi P, Kaur I, Dogra S. Efficacy and safety of combination acitretin and pioglitazone therapy in patients with moderate to severe chronic plaque-type psoriasis: a randomized, double-blind, placebo-controlled clinical trial. Arch Dermatol 2009;145:387-93.
86. Dreyer C, Krey G, Keller H, et al. Control of the peroxisome beta-oxidation pathway by a novel family of nuclear hormone receptors. Cell 1992;68:879-87.
87. Vu-Dac N, Schoonjans K, Laine B, et al. Negative regulation of the human apolipoprotein A-I promoter by fibrates can be attenuated by the interaction of the peroxisome proliferator-activated receptor with its response element. J Biol Chem 1994;269:31012-8.
88. Hertz R, Bishara-Shieban J, Bar-Tana J. Mode of action of peroxisome proliferators as hypolipidemic drugs: suppression of apolipoprotein C-III. J Biol Chem 1995;270:13470-5.
89. Rodriguez JC, Gil-Gomez G, Hegardt FG, et al. Peroxisome proliferator-activated receptor mediates induction of the mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase gene by fatty acids. J Biol Chem 1994;269:18767-72.
90. Oliver WR, Shenk JL, Snaith MR, et al. A selective peroxisome proliferator-activated receptor delta agonist promotes reverse cholesterol transport. Proc Natl Acad Sci U S A 2001;98:5306-11.
91. Leibowitz MD, Fievet C, Hennuyer N, et al. Activation of PPARdelta alters lipid metabolism in db/db mice. FEBS Lett 2000;473:333-6.
92. Clark RB. The role of PPARs in inflammation and immunity. J Leukoc Biol 2002;71:388-400.
93. Hoffmann C, Lorenz K, Braithwaite SS, et al. Altered gene expression for tumor necrosis factor-alpha and its receptors during drug and dietary modulation of insulin resistance. Endocrinology 1994;134: 264-70.
94. Ricote M, Li AC, Willson TM, Kelly CJ, Glass CK. The peroxisome proliferator-activated receptor-gamma is a negative regulator of macrophage activation. Nature 1998;391:79-82.
95. Jiang CY, Ting AT, Seed B. PPAR-gamma agonists inhibit production of monocyte inflammatory cytokines. Nature 1998;391:82-6.
96. Martin H. Role of PPAR-gamma in inflammation. Prospects for therapeutic intervention by food components. Mutat Res 2009;669: 1-7.
97. Gosset P, Charbonnier AS, Delerive P, et al. Peroxisome proliferator-activated receptor gamma activators affect the maturation of human monocyte-derived dendritic cells. Eur J Immunol 2001;31:2857-65.
98. Faveeuw C, Fougeray S, Angeli V, et al. Peroxisome proliferator-activated receptor gamma activators inhibit interleukin-12 production in murine dendritic cells. FEBS Lett 2000;486:261-6.
99. Westergaard M, Henningsen J, Johansen C, et al. Expression and localization of peroxisome proliferator-activated receptors and nuclear factor kappaB in normal and lesional psoriatic skin. J Invest Dermatol 2003;121:1104-17.
100. Plager DA, Leontovich AA, Henke SA, et al. Early cutaneous gene transcription changes in adult atopic dermatitis and potential clinical implications. Exp Dermatol 2007;16:28-36.
101. Matsuura H, Adachi H, Smart RC, Xu X, Arata J, Jetten AM. Correlation between expression of peroxisome proliferator-activated receptor beta and squamous differentiation in epidermal and tracheobronchial epithelial cells. Mol Cell Endocrinol 1999;147: 85-92.
102. Rivier M, Safonova I, Lebrun P, Griffiths CE, Ailhaud G, Michel S. Differential expression of peroxisome proliferator-activated receptor subtypes during the differentiation of human keratinocytes. J Invest Dermatol 1998;111:1116-21.
103. Westergaard M, Henningsen J, Svendsen ML, et al. Modulation of keratinocyte gene expression and differentiation by PPAR-selective ligands and tetradecylthioacetic acid. J Invest Dermatol 2001;116: 702-12.
104. Lo Verme J, Fu J, Astarita G, et al. The nuclear receptor peroxisome proliferator-activated receptor-alpha mediates the anti-inflammatory actions of palmitoylethanolamide. Mol Pharmacol 2005;67:15-9.

105. Komuves LG, Hanley K, Man MQ, Elias PM, Williams ML, Feingold KR. Keratinocyte differentiation in hyperproliferative epidermis: topical application of PPARalpha activators restores tissue homeostasis. J Invest Dermatol 2000;115:361-7.
106. Scott IR, Harding CR. Filaggrin breakdown to water binding compounds during the development of the rat stratum corneum is controlled by the water activity of the environment. Dev Biol 1986;115:84-92.
107. Di-Poi N, Tan NS, Michalik L, Wahli W, Desvergne B. Antiapoptotic role of PPARbeta in keratinocytes via transcriptional control of the Akt1 signaling pathway. Mol Cell 2002;10:721-33.
108. Demerjian M, Man MQ, Choi EH, et al. Topical treatment with thiazolidinediones, activators of peroxisome proliferator-activated receptor-gamma, normalizes epidermal homeostasis in a murine hyperproliferative disease model. Exp Dermatol 2006;15:154-60.
109. Kuenzli S, Saurat JH. Effect of topical PPARbeta/delta and PPARgamma agonists on plaque psoriasis. A pilot study. Dermatology 2003;206:252-6.
110. Kuenzli S, Saurat JH. Peroxisome proliferator-activated receptors in cutaneous biology. Br J Dermatol 2003;149:229-36.
111. Kuenzli S, Saurat JH. Peroxisome proliferator-activated receptors as new molecular targets in psoriasis. Curr Drug Targets 2004;3:205-11.
112. Palomba S, Falbo A, Orio F, Zullo F. Insulin-sensitizing agents and reproductive function in polycystic ovary syndrome patients. Curr Opin Obstet Gynecol 2008;20:364-73.
113. Msika P, De Belilovsky C, Chadoutaud B, Nicolas JF. New natural PPAR-alpha agonist for childhood atopic dermatitis: dermocorticoid-sparing and quality of life improvement [abstract]. J Am Acad Dermatol 2007;56:AB67.
114. Hanley K, Ng DC, He SS, et al. Oxysterols induce differentiation in human keratinoytes and increase AP-1-dependent involucrin transcrition. J Invest Dermatol 2000;114:545-53.
115. Hanley K, Jiang Y, He SS, et al. Keratinocyte differentiation is stimulated by activators of the nuclear hormone receptor PPARalpha. J Invest Dermatol 1998;110:368-75.
116. Mueller M, Lukas B, Novak J, Simoncini T, Genazzani AR, Jungbauert A. Oregano: a source for peroxisome proliferator-activated receptor gamma antagonists. J Agri Food Chem 2008;56:11621-30.
117. Zhou XR, Sun CH, Liu JR, Zhao D. Dietary conjugated linoleic acid increases PPAR gamma gene expression in adipose tissue of obese rat and improves insulin resistance. Growth Horm IGF Res 2008;18: 361-8.
118. Michalik L, Wahli W. Peroxisome proliferator-activated receptors (PPARs) in skin health, repair and disease. Biochim Biophys Acta 2007;1771:991-8.
119. Michalik L, Desvergne NS, Tan NS, et al. Impaired skin wound healing in peroxisome proliferator-activated receptor PPARalpha and PPARbeta mutant mice. J Cell Biol 2001;154:799-814.
120. Nijsten T, Geluyckens E, Colpaert C, et al. Peroxisome proliferator-activated receptors in squamous cell carcinoma and its precursors. J Cutan Pathol 2005;32:340-7.
121. Kippenberger S, Loitsch SM, Grundmann-Kollmann M, et al. Activators of peroxisome proliferator-activated receptors protect human skin from ultraviolet-B-light-induced inflammation. J Invest Dermatol 2001;117:1430-6.
122. Mossner R, Schulz U, Kruger U, et al. Activators of peroxisome proliferator-activated receptor gamma inhibit cell growth in malignant melanoma. J Invest Dermatol 2002;119:576-82.
123. Grabacka M, Plonka PM, Urbanska K, Reiss K. Peroxisome proliferator-activated receptor alpha activation decreases metastatic potential of melanoma cells in vitro via down regulation of Akt. Clin Cancer Res 2006;12:3028-36.
124. Grabacka M, Placha W, Plonka PM, et al. Inhibition of melanoma metastases by fenofibrate. Arch Dermatol Res 2004;296:54-8.
125. Hoek KS, Schlegel NC, Brafford P, et al. PPAR gamma regulates MITF and beta catenin expression and promotes a differentiated phenotype. Pig Cell Mel Res 2008;3:388-96.
126. Lee JY, Plakidas A, Lee WH, Heikkinen A, Chanmugam P, Bray G, Hwang DH. Differential modulation of Toll-like receptors by fatty acids: preferential inhibition by n-3 polyunsaturated fatty acids. J Lipid Res 2003;44:479-86.
127. Takeda K, Kaisho T, Akira S. Toll-like receptors. Annu Rev Immunol 2003;21:335-76.
128. Netea MG, van der Graaf C, Van der Meer JWM, Jan Kullberg B. Toll-like receptors and the host defense against microbial pathogens: bringing specificity to the innate-immune system. J Leukoc Biol 2004;75:749-55.
129. Lee JY, Zhao L, Youn HS, et al. Saturated fatty acid activates but polyunsaturated fatty acid inhibits toll-like receptor 2 dimerized with toll-like receptor 6 or 1. J Bio Chem 2004;279:16971-9.
130. Weidinger S, Novak N, Klopp N, et al. Lack of association between Toll-like receptor 2 and Toll-like receptor 4 polymorphisms and atopic eczema. J Allergy Clin Immunol 2006;118:277-9.
131. Aoki S, Yaoita H, Kitajima Y. An elevated level of autoantibodies against 48-50 kd keratins in the serum of patients with psoriasis. J Invest Dermatol 1989;92:179-83.
132. Wu C, Luan Q, Lit C, Zheng Z. Effects of antikeratin 16 antibodies on the expression of Toll-like receptors 2 and 4 in keratinocytes. Clin Exp Dermatol 2008;34:236-9.
133. Oeff MK, Seltmann H, Hiroi N, et al. Differential regulation of toll-like receptor and CD14 pathways by retinoids and corticosteroids in human sebocytes. Dermatology 2006;213:266.
134. Nakatsuji T, Kao MC, Fang JY, et al. Antimicrobial property of lauric acid against Propionibacterium acnes: its therapeutic potential for inflammatory acne vulgaris. J Invest Dermatol 2009;129:2480-8.