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Eicosanoids and Keratinocytes in Wound Healing

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Significance: Eicosanoids are biologically active lipid mediators derived from arachidonic acid that are important in injury and inflammatory responses. Cyclooxygenase-1 and cyclooxygenase-2 mediate the production of prostanoids, whereas 5-lipoxygenase mediates the production of leukotrienes and hydroxyeicosatetraenoic acids. These lipid mediators have traditionally been known to recruit cells of the immune system to a site of injury and inflammation. However, they also interact with various cells that are resident to the wound bed, including modulation of keratinocyte activity.

Recent Advances: Recent work has identified multiple prostanoid and leukotriene receptors on keratinocytes, indicating that eicosanoids directly interact with them. Recent work also shows that keratinocytes are capable of producing prostanoids and leukotrienes.

Critical Issues: Much of the critical work has been performed in cell culture and mouse *in vivo* models. This has greatly expanded our understanding of the eicosanoid interactions with keratinocytes and wound healing in general. However, few of these *in vivo* models have been able to critically evaluate keratinocyte migration and re-epithelialization.

Future Directions: As research continues in this exciting field, the cellular pathways stimulated by the eicosanoids will become better defined. Future research with excisional wound models in mice and pigs and *ex vivo* human skin models will better isolate the contribution of eicosanoid-mediated effects on keratinocyte migration and re-epithelialization.

SCOPE AND SIGNIFICANCE

EICOSANOIDS ARE INFLAMMATORY lipid mediators that have been implicated in a variety of diseases such as neoplasms, inflammatory disease, and wound healing. They serve an important role in modulating the inflammatory response, but they also directly interact with keratinocytes. Keratinocyte migration and re-epithelialization is one of the important initial steps in wound healing. In this study, we review the interaction between eicosanoids and keratinocyte as it pertains to wound repair.

TRANSLATIONAL RELEVANCE

Research within wound healing depends heavily on translational models that encompass both cell culture and animal-based models. These serve as important preclinical steps to help identify signaling pathways and mechanisms before development of therapeutic strategies. In this study, the influence of eicosanoids in keratinocyte biology is reviewed with comparative discussion of the COX-1/COX-2 pathways and the 5-LOX pathway in the synthesis of eicosanoids. In doing so, the current state of knowledge is

discussed and, more importantly, knowledge gaps are identified to stimulate further research.

CLINICAL RELEVANCE

Modulation of the eicosanoid pathway is clinically important. Several medications that modulate this pathway are already approved by the Food and Drug Administration for clinical use. This article overviews the importance of eicosanoids in wound healing, particularly in relation to re-epithelialization. As such, it is hoped that the information presented here will stimulate clinical investigation of adapting existing drugs in novel ways for wound therapy. Modulators of eicosanoid synthesis may serve a promising and novel role in the clinical therapy of wounds.

OVERVIEW OF EICOSANOIDS

Eicosanoids represent a family of lipids derived from arachidonic acid (AA) that are biologically active mediators. AA is released from the cell membrane through activation of phospholipases due to various stimuli. AA is subsequently metabolized through three enzyme pathways to generate eicosanoids due to cyclooxygenase (COX), leukotrienes and hydroxyeicosatetraenoic acids (HETEs) due to lipoxygenase (LOX), or HETEs and epoxyeicosatrienoic acids through the cytochrome P450-dependant epoxidases. Figure 1 depicts a broad

Figure 1. Schematic of the major eicosanoid synthesis pathways that involve the lipoxygenase (LOX) and cyclooxygenase (COX) pathways. LTA4, leukotrienes A4; LTB4, leukotriene B4; HETE, hydroxyeicosatetraenoic acid; PGG2, prostaglandin G2; PGH2, prostaglandin H2; PGI2, prostacyclin; PGD2, prostaglandin D2; PGE2, prostaglandin E2; PGF2 α , prostaglandin F2 α ; TXA2, thromboxane A2.

schematic for eicosanoid synthesis through the COX and LOX pathways.

The prostanoids are generated through the action of the COX enzymes. There are two forms of cyclooxygenases, COX-1 and COX-2.¹ The family of bioactive prostanoids include prostaglandins (PGD2, PGE2, and PGF2 α), prostacyclin (PGI2), and thromboxane A2.² The prostanoid receptors were pharmacologically characterized based on their ability to bind PDG2, PGE2, PGF2 α , PGI2, and thromboxane A2 as DP, EP, FP, IP, and TP receptors, respectively.² The DP receptors are subdivided into DP1 and DP2 and the EP receptors are subdivided into EP1, EP2, EP3, and EP4.² These receptors are G-protein-coupled transmembrane receptors that signal through various pathways, including cAMP, ERK, and AKT.² Keratinocytes express both COX-1 and COX-2, with COX-2 primarily found in the suprabasilar keratinocytes,² and have the ability to synthesize multiple prostanoids.³ Keratinocytes express multiple prostanoid receptors, such as EP1,⁴ EP2,^{4,5} EP3,⁵ and low levels of EP4 (based on mRNA expression).⁵

The LOX enzymes are structurally related dioxygenases involved in the production of fatty acid hydroperoxides by acting on polyunsaturated fatty acids.⁶ Humans express multiple LOXs in the skin.⁷ The nomenclature is based on the specificity of action for each enzyme in the family.⁸ For example, 5-LOX oxygenates AA at carbon-5 and 12-LOX at the carbon-12 position.

The leukotrienes are a subfamily of lipid mediators that are generated through the action of 5-LOX on AA.⁹ Leukotriene A4 (LTA4) is the first product of 5-LOX and this leads to the generation of LTB4, LTC4, LTD4, and LTE4.⁹ There are multiple leukotriene receptors, including the LTB4 receptor type-1 (BLT1), BLT2, and the CysLT family of receptors that act as G-protein-coupled transmembrane receptors.⁹ Murine keratinocytes have been shown to produce LTB4.¹⁰ However, studies in human keratinocytes remain mixed with one study that showed a lack of expression of 5-LOX or the ability for endogenous LTB4 production,¹¹ while others noted expression of 5-LOX in the epidermis¹² and documented LTB4¹³ and 5-HETE release.¹³ Regardless, keratinocytes can produce LTB4 in the presence of LTA4 as they express the LTA4 hydrolase necessary for the synthesis of LTB4.¹⁴ Keratinocytes express the BLT1¹⁵ and BLT2¹⁶ leukotriene-sensitive receptors.

Eicosanoids play an important role in wound healing (Fig. 2). Keratinocytes are capable of both producing and responding to eicosanoids in the wound.

Figure 2. Eicosanoids modulate keratinocyte proliferation and migration, as well as stratum corneum barrier formation.

DISCUSSION

Eicosanoids in the wound microenvironment

Eicosanoids are abundant in the wound bed early after tissue injury.¹⁷ Multiple cells typically found in the wound bed are capable of eicosanoid synthesis.^{3,8,18,19} Bacteria can induce synthesis of various eicosanoids,²⁰ although their contribution in acute and chronic wounds remains to be further studied. Free radical-induced conversion of AA into the isoprostanes,²¹ which serve as prostaglandin analogs, augments the eicosanoid levels in the wound.

Prostanoids

Keratinocyte proliferation. Prostanoids increase the proliferation of epithelial cells (Table 1) through both direct and indirect mechanisms. PGE1 and PGI1 analogues increase keratinocyte proliferation,^{22,23} as does PGE2.⁵ Furthermore, the stimulation of keratinocyte EP2 and EP4 receptors promotes keratinocyte proliferation.⁵ PGE1 can stimulate keratinocyte proliferation indirectly as well. PGE1 can induce IL-6 production in fibroblasts, which can in turn stimulate keratinocyte proliferation.²³

Keratinocyte migration. Several studies have examined the role of prostanoids in keratinocyte migration (Table 1). In mice, COX-2 expression was found to increase in the hyperplastic keratinocytes at the edge of an incisional wound²⁴ and in keratinocytes migrating from the edge of an incisional wound.²⁵ COX-2 expression also increased in underlying keratinocytes in an abrasion injury model where the superficial stratum corneum was removed without direct injury to the underlying epidermis.²⁶ The results on the effects of pharmacological inhibition of COX-2 are mixed in mouse incisional wounds *in vivo* with one study showing an early transient decrease in re-epithelialization,²⁴ while another study showed increased re-epithelialization.²⁷ Furthermore, two other studies did not note any effects on skin wound healing,^{28,29} and yet another study demonstrated reduced tensile strength in mice with either COX-1 or COX-2 genes knocked out.³⁰ None of these studies specifically evaluated keratinocyte re-epithelialization. It is unclear how well incisional wounds and unsplinted excisional wounds in mice mimic human wounds, since wounds in mice involve significant contraction, while human wounds rely heavily on re-epithelialization and granulation tissue formation.³¹

Taken together, COX-2 is upregulated in keratinocytes adjacent to a wound and prostanoids increase their proliferation. However, their role in re-epithelialization and keratinocyte migration remains unclear. Future studies in wounds that more closely replicate human wounds, such as porcine models and *ex vivo* human skin models, are needed to better identify the influence of COX-2-derived products on keratinocyte migration.

LOX products

Keratinocyte proliferation. Few studies have evaluated the association between leukotrienes and keratinocyte proliferation. Multiple leukotrienes have been shown to increase DNA synthesis rates in cultured human keratinocytes.³² Topical

Table 1. Interaction of different eicosanoids with keratinocytes

Eicosanoid	Proliferation	Migration	Barrier Formation
Prostanoids			
Prostaglandin D2	NE	NE	Promotes barrier formation
Prostaglandin E1	Increase	NE	NE
Prostaglandin E2	Increase	Unclear	Mixed
Prostaglandin I1 analogues	Increase	NE	NE
Leukotrienes			
Leukotriene B4	Possible increase	Unclear	NE
HETE			
12-HETE	NE	Possible increase	Likely promotes barrier formation based on genetic studies

HETE, hydroxyeicosatetraenoic acid; NE, not evaluated.

application of LTB₄ induced hyperproliferation in humans when applied to psoriatic skin, but not in uninvolved skin.³³ Yet, the use of a 5-LOX inhibitor did not alter keratinocyte proliferation³⁴ in cell culture nor was it noted to reduce epidermal proliferation when given orally to patients with psoriasis.³⁵ Therefore, while leukotrienes may be capable of increasing proliferation, the inhibition of their effects may not be sufficient to reduce keratinocyte proliferation. Further studies that specifically evaluate the role of leukotrienes and its inhibitors are needed to better delineate their effects on keratinocyte proliferation.

Keratinocyte migration. In murine keratinocytes, activation of the BTL2 receptor increased ERK phosphorylation and induced their migration,³⁶ but similar studies in human keratinocytes are lacking. Keratinocytes have been shown to increase the expression of matrix metalloproteinase-1 (MMP-1) in response to stimulation of the LTB₄-sensitive BLT2.¹⁶ Upregulation of MMP-1 has been associated with a migratory phenotype in keratinocytes,³⁷ but the direct effect of BLT2 receptor activation on human keratinocyte migration has not been evaluated. Studies in 5-LOX-deficient mice showed accelerated wound healing, but the re-epithelialization rates did not appear to differ between the 5-LOX and wild-type mice.³⁸ It is not clear whether prostanoid levels were elevated in the 5-LOX knockout mice in light of other studies that have shown shunting from the 5-LOX pathway into the COX-1/COX-2 pathway with 5-LOX inhibition.³⁹ Regardless, the lack of 5-LOX activity was not a detriment against wound re-epithelialization. 12-HETE is produced in the epidermis and is bound by keratinocytes⁴⁰ and appears to stimulate keratinocyte chemotaxis toward it.⁴¹ Taken together, leukotrienes may increase murine keratinocyte migration, but its role in human keratinocytes remains unstudied. The role of HETEs in keratinocyte migration needs further elucidation as well.

Barrier formation

An important step in wound repair after re-epithelialization is the formation of a mature epidermal barrier. This depends on the terminal differentiation of keratinocytes and the eventual formation of a mature stratum corneum. The eicosanoids have an important role in the formation of the epidermal barrier (Table 1).

The prostanoids accelerate recovery of the epidermal barrier.^{42,43} Indomethacin, a nonselective inhibitor of COX-1 and COX-2, decreased transepidermal

TAKE-HOME MESSAGES

- (1) Eicosanoids are lipid mediators that are endogenously produced, present in wounds, and directly interact with keratinocytes.
- (2) Prostanoids increase keratinocyte proliferation.
- (3) 12R-LOX and eLOX-3 are important for synthesis of ceramides and development of the stratum corneum barrier.

water loss (TEWL) recovery after mechanical disruption of the barrier in mice.⁴² Selective inhibition of COX-1 and COX-2 suggested that COX-1-modulated PGD₂ was important for barrier recovery.⁴⁴ PGD₂ was shown to accelerate barrier recovery in mice after mechanical disruption of the stratum corneum based on the recovery of the TEWL.^{42,45} Studies on PGE₂ were mixed with one study showing no effect⁴² and another showing improvement of the barrier function.⁴⁵ Future studies with disruption of the human skin barrier, perhaps through tape stripping, would help evaluate if the findings in mice extend to humans.

The lipoxygenases are important in the development of the skin barrier. In particular, 12-LOX and epidermal lipoxygenase-3 (eLOX3) are important for ceramide synthesis and mature barrier formation.⁴⁶ This is confirmed by the disrupted barrier in both 12R-LOX-deficient^{47,48} and eLOX3-deficient⁴⁹ mice. Consistent with the implication that LOX enzymes are important for maintaining epidermal homeostasis, mutations in the genes for eLOX-3 and 12R-LOX have been associated with autosomal recessive, non-bullous congenital ichthyosiform erythroderma in humans.⁵⁰

SUMMARY

Eicosanoids play an important role in modulating keratinocyte biology. This lipid family has functions that are plastic and move beyond serving as inflammatory mediators. The current state of knowledge is building with a better understanding of how the prostanoids, leukotrienes, and the LOX products interact with the keratinocytes in the wound microenvironment. Further research is needed in human cells and human tissue and the modulation of eicosanoid synthesis is promising for further investigation.

AUTHOR DISCLOSURE AND GHOSTWRITING

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REFERENCES

- Smith WL, Langenbach R. Why there are two cyclooxygenase isozymes. *J Clin Invest* 2001;107:1491–1495.
- Hirata T, Narumiya S. Prostanoids as regulators of innate and adaptive immunity. *Adv Immunol* 2012;116:143–174.
- Ziboh VA, Miller CC, Cho Y. Significance of lipoxygenase-derived monohydroxy fatty acids in cutaneous biology. *Prostaglandins Other Lipid Mediat* 2000;63:3–13.
- Konger RL, Billings SD, Thompson AB, et al. Immunolocalization of low-affinity prostaglandin E receptors, EP and EP, in adult human epidermis. *J Invest Dermatol* 2005;124:965–970.
- Konger RL, Malaviya R, Pentland AP. Growth regulation of primary human keratinocytes by prostaglandin E receptor EP2 and EP3 subtypes. *Biochim Biophys Acta* 1998;1401:221–234.
- Strassburg K, Huijbrechts AM, Kortekaas KA, et al. Quantitative profiling of oxylipins through comprehensive LC-MS/MS analysis: application in cardiac surgery. *Anal Bioanal Chem* 2012;404:1413–1426.
- Krieg P, Furstenberger G. The role of lipoxygenases in epidermis. *Biochim Biophys Acta* 2014;1841:390–400.
- Sivamani RK, Garcia MS, Isseroff RR. Wound reepithelialization: modulating keratinocyte migration in wound healing. *Front Biosci* 2007;12:2849–2868.
- Di Gennaro A, Haeggström JZ. The leukotrienes: immune-modulating lipid mediators of disease. *Adv Immunol* 2012;116:51–92.
- Zhu Y, Wang XR, Peng C, et al. Induction of leukotriene B(4) and prostaglandin E(2) release from keratinocytes by protease-activated receptor-2-activating peptide in ICR mice. *Int Immunopharmacol* 2009;9:1332–1336.
- Breton J, Woolf D, Young P, Chabot-Fletcher M. Human keratinocytes lack the components to produce leukotriene B4. *J Invest Dermatol* 1996;106:162–167.
- Ziboh VA, Casebolt TL, Marcelo CL, Voorhees JJ. Biosynthesis of lipoxygenase products by enzyme preparations from normal and psoriatic skin. *J Invest Dermatol* 1984;83:426–430.
- Grabbe J, Czarnetzki BM, Mardin M. Release of lipoxygenase products of arachidonic acid from freshly isolated human keratinocytes. *Arch Dermatol Res* 1984;276:128–130.
- Iversen L, Ziboh VA, Shimizu T, et al. Identification and subcellular localization of leukotriene A4-hydrolase activity in human epidermis. *J Dermatol Sci* 1994;7:191–201.
- Kanda N, Watanabe S. Leukotriene B(4) enhances tumour necrosis factor-alpha-induced CCL27 production in human keratinocytes. *Clin Exp Allergy* 2007;37:1074–1082.
- Kim C, Ryu HC, Kim JH. Low-dose UVB irradiation stimulates matrix metalloproteinase-1 expression via a BLT2-linked pathway in HaCaT cells. *Exp Mol Med* 2010;42:833–841.
- Gronert K. Lipid autacoids in inflammation and injury responses: a matter of privilege. *Mol Interv* 2008;8:28–35.
- Jain A, Bronneke S, Kolbe L, Stab F, Wenck H, Neufang G. TRP-channel-specific cutaneous eicosanoid release patterns. *Pain* 2011;152:2765–2772.
- Nicolaou A. Eicosanoids in skin inflammation. *Prostaglandins Leukot Essent Fatty Acids* 2013;88:131–138.
- Eberhard J, Jepsen S, Pohl L, Albers HK, Acil Y. Bacterial challenge stimulates formation of arachidonic acid metabolites by human keratinocytes and neutrophils *in vitro*. *Clin Diagn Lab Immunol* 2002;9:132–137.
- Yeoh-Ellerton S, Stacey MC. Iron and 8-isoprostane levels in acute and chronic wounds. *J Invest Dermatol* 2003;121:918–925.
- Kaneko F, Zhang JZ, Maruyama K, et al. Prostaglandin I1 analogues, SM-10902 and SM-10906, affect human keratinocytes and fibroblasts *in vitro* in a manner similar to PGE1: therapeutic potential for wound healing. *Arch Dermatol Res* 1995;287:539–545.
- Zhang JZ, Maruyama K, Iwatsuki K, Ono I, Kaneko F. Effects of prostaglandin E1 on human keratinocytes and dermal fibroblasts: a possible mechanism for the healing of skin ulcers. *Exp Dermatol* 1994;3:164–170.
- Muller-Decker K, Hirschner W, Marks F, Furstenberger G. The effects of cyclooxygenase isozyme inhibition on incisional wound healing in mouse skin. *J Invest Dermatol* 2002;119:1189–1195.
- Blomme EA, Chinn KS, Hardy MM, et al. Selective cyclooxygenase-2 inhibition does not affect the healing of cutaneous full-thickness incisional wounds in SKH-1 mice. *Br J Dermatol* 2003;148:211–223.
- Hardy MM, Blomme EA, Lisowski A, et al. Selective cyclooxygenase-2 inhibition does not alter keratinocyte wound responses in the mouse epidermis after abrasion. *J Pharmacol Exp Ther* 2003;304:959–967.
- Santuzzi CH, Buss HF, Pedrosa DF, Freire MO, Nogueira BV, Goncalves WL. Combined use of low level laser therapy and cyclooxygenase-2 selective inhibition on skin incisional wound reepithelialization in mice: a preclinical study. *An Bras Dermatol* 2011;86:278–283.
- Hazut O, Shaashua L, Benish M, et al. The effect of beta-adrenergic blockade and COX-2 inhibition on healing of colon, muscle, and skin in rats undergoing colonic anastomosis. *Int J Clin Pharmacol Ther* 2011;49:545–554.
- Cahill RA, Sheehan KM, Scanlon RW, Murray FE, Kay EW, Redmond HP. Effects of a selective cyclooxygenase 2 inhibitor on colonic anastomotic and skin wound integrity. *Br J Surg* 2004;91:1613–1618.
- Laulederkind SJ, Thompson-Jaeger S, Goorha S, et al. Both constitutive and inducible prostaglandin H synthase affect dermal wound healing in mice. *Lab Invest* 2002;82:919–927.
- Galiano RD, Michaels Jt, Dobryansky M, Levine JP, Gurtner GC. Quantitative and reproducible murine model of excisional wound healing. *Wound Repair Regen* 2004;12:485–492.
- Kragballe K, Desjarlais L, Voorhees JJ. Leukotrienes B4, C4 and D4 stimulate DNA synthesis in cultured human epidermal keratinocytes. *Br J Dermatol* 1985;113:43–52.
- Bauer FW, van de Kerkhof PC, Maassen-de Grood RM. Epidermal hyperproliferation following the induction of microabscesses by leukotriene B4. *Br J Dermatol* 1986;114:409–412.
- Hegemann L, Hatzelmann A, Grewig S, Schmidt BH. Potent antagonism of calmodulin activity *in vitro*, but lack of antiproliferative effects on keratinocytes by the novel leukotriene biosynthesis inhibitor MK-886. *Br J Dermatol* 1995;133:41–47.
- de Jong EM, van Vlijmen IM, Scholte JC, et al. Clinical and biochemical effects of an oral

- leukotriene biosynthesis inhibitor (MK886) in psoriasis. *Skin Pharmacol* 1991;4:278–285.
36. Iizuka Y, Yokomizo T, Terawaki K, Komine M, Tamaki K, Shimizu T. Characterization of a mouse second leukotriene B₄ receptor, mBLT2: BLT2-dependent ERK activation and cell migration of primary mouse keratinocytes. *J Biol Chem* 2005;280:24816–24823.
 37. Pilcher BK, Dumin JA, Sudbeck BD, Krane SM, Welgus HG, Parks WC. The activity of collagenase-1 is required for keratinocyte migration on a type I collagen matrix. *J Cell Biol* 1997;137:1445–1457.
 38. Brogliato AR, Moor AN, Kesl SL, et al. Critical role of 5-lipoxygenase and heme oxygenase-1 in wound healing. *J Invest Dermatol* 2014;134:1436–1445.
 39. Mohebbati A, Milne GL, Zhou XK, et al. Effect of zileuton and celecoxib on urinary LTE₄ and PGE-M levels in smokers. *Cancer Prev Res (Phila)* 2013;6:646–655.
 40. Suss R, Arenberger P, Gross EC, Ruzicka T. Regulation of 12(S)-hydroxyeicosatetraenoic acid (12(S)-HETE) binding sites on human epidermal cells by interferon-gamma. *Exp Cell Res* 1990;191:204–208.
 41. Ruzicka T. The role of the epidermal 12-hydroxyeicosatetraenoic acid receptor in the skin. *Eicosanoids* 1992;5 Suppl:S63–S65.
 42. Honma Y, Arai I, Sakurai T, et al. Effects of indomethacin and dexamethasone on mechanical scratching-induced cutaneous barrier disruption in mice. *Exp Dermatol* 2006;15:501–508.
 43. Futaki N, Arai I, Sugimoto M, et al. Role of prostaglandins on mechanical scratching-induced cutaneous barrier disruption in mice. *Exp Dermatol* 2007;16:507–512.
 44. Honma Y, Arai I, Futaki N, et al. Cyclooxygenase-1 inhibition delays recovery of the cutaneous barrier disruption caused by mechanical scratching in mice. *Br J Dermatol* 2007;156:1178–1187.
 45. Honma Y, Arai I, Hashimoto Y, et al. Prostaglandin D₂ and prostaglandin E₂ accelerate the recovery of cutaneous barrier disruption induced by mechanical scratching in mice. *Eur J Pharmacol* 2005;518:56–62.
 46. Furstenberger G, Epp N, Eckl KM, et al. Role of epidermis-type lipoxygenases for skin barrier function and adipocyte differentiation. *Prostaglandins Other Lipid Mediat* 2007;82:128–134.
 47. Zheng Y, Yin H, Boeglin WE, et al. Lipoxygenases mediate the effect of essential fatty acid in skin barrier formation: a proposed role in releasing omega-hydroxyceramide for construction of the corneocyte lipid envelope. *J Biol Chem* 2011;286:24046–24056.
 48. Epp N, Furstenberger G, Muller K, et al. 12R-lipoxygenase deficiency disrupts epidermal barrier function. *J Cell Biol* 2007;177:173–182.
 49. Krieg P, Rosenberger S, de Juanes S, et al. Alox3 knockout mice reveal a function of epidermal lipoxygenase-3 as hepoxilin synthase and its pivotal role in barrier formation. *J Invest Dermatol* 2013;133:172–180.
 50. Jobard F, Lefevre C, Karaduman A, et al. Lipoxygenase-3 (ALOXE3) and 12(R)-lipoxygenase (ALOX12B) are mutated in non-bullous congenital ichthyosiform erythroderma (NCIE) linked to chromosome 17p13.1. *Hum Mol Genet* 2002;11:107–113.

Abbreviations and Acronyms

AA = arachidonic acid
 BLT1 = leukotriene B₄ receptor type-1
 BLT2 = leukotriene B₄ receptor type-2
 cAMP = cyclic AMP
 COX-1 = cyclooxygenase-1
 COX-2 = cyclooxygenase-2
 eLOX3 = epidermal lipoxygenase-3
 ERK = extracellular signal-regulated kinases
 HETE = hydroxyeicosatetraenoic acid
 HPETE = hydroperoxyeicosatetraenoic acids
 LTA₄ = leukotriene A₄
 LTB₄ = leukotriene B₄
 LTBC₄ = leukotriene C₄
 LTBD₄ = leukotriene D₄
 LTBE₄ = leukotriene E₄
 LOX = lipoxygenase
 MMP-1 = matrix metalloproteinase-1
 PGD₂ = prostaglandin D₂
 PGE₂ = prostaglandin E₂
 PGI₂ = prostacyclin
 PGF₂α = prostaglandin F₂α
 TEWL = transepidermal water loss