

Leukotrienes orchestrating allergic skin inflammation

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Abstract: Leukotrienes constitute a group of lipid mediators, which may be subdivided into two groups, with leukotriene B₄ on the one hand and cysteinyl leukotrienes on the other. Although leukotrienes are abundantly expressed in skin affected by diverse chronic inflammatory diseases, including atopic dermatitis, psoriasis, pemphigus vulgaris and bullous pemphigoid, their pathological roles in these diseases have remained elusive. Recent data now reveal that both leukotriene B₄ and cysteinyl leukotrienes are indispensable in the pathogenesis of atopic dermatitis, with leukotriene B₄ initiating the recruitment of inflammatory cells, particularly neutrophils and T_H2 cells into the skin, and cysteinyl leukotrienes later

inducing characteristic structural alterations of chronically affected skin, specifically skin fibrosis and keratinocyte proliferation. Thus, these results reveal a sequential cooperation of LTB₄ and cysteinyl leukotrienes to initiate and perpetuate allergic skin inflammation. These new insights highlight leukotrienes as promising therapeutic targets in allergic skin inflammation and should encourage more research into the role of leukotrienes in other inflammatory skin diseases.

Key words: atopic dermatitis – inflammation – leukotrienes – lipid mediators – neutrophils

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Introduction

Leukotrienes are abundantly expressed in the skin in diverse inflammatory skin diseases and have been suggested to contribute to the pathogenesis of these diseases, although direct evidence in support of this notion is scarce. Recently, by use of a sophisticated mouse model, some light has finally been shed on the role of leukotrienes in atopic dermatitis (AD), indicating that leukotrienes play a crucial role in its pathogenesis. Furthermore, these results suggest that different classes of leukotrienes each play distinct and essential roles in this disease. In this *Viewpoint*, we will highlight these latest insights into the role leukotrienes of in (AD).

Leukotrienes and their receptors

Leukotrienes (LTs) are short-lived lipid mediators, which act in an autocrine and paracrine manner. They can be subdivided into two groups: the first group is represented by leukotriene B₄ (LTB₄) alone. The second group is constituted by the cysteinyl leukotrienes (cys-LTs), namely leukotriene C₄ (LTC₄), leukotriene D₄ (LTD₄) and leukotriene E₄ (LTE₄) (1,2).

Leukotrienes are not intracellularly stored, but ultra-rapidly produced *de novo* and released within minutes upon cell activation. Numerous stimuli can induce leukotriene release, such as immune complexes, cytokines, complement and TLR activation (1).

For biosynthesis of LTs, arachidonic acid, esterified to membrane phospholipids, is released from its ester bond by hydrolysis catalysed by phospholipase A₂. The activity of phospholipase A₂ is tightly controlled and poses a key checkpoint for the biosynthesis of leukotrienes (3). Afterwards, 5-lipoxygenase (5-LO) converts arachidonic acid to leukotriene A₄ (LTA₄), the last common precursor of all LTs (Fig. 1) (1,4,5). At this point, the biosynthesis pathways of LTB₄ and cys-LTs diverge, with LTA₄ hydrolase (LTA₄H) dehydrating LTA₄ to LTB₄, and LTC₄ synthase (LTC₄S) conjugating glutathione to LTA₄ to yield LTC₄, which can be further converted to LTD₄ and finally LTE₄ by sequential

cleavage of the glutathionyl moiety through γ -glutamyl transpeptidase and dipeptidase (Fig. 1).

Significant expression of 5-LO is restricted to myeloid cells, rendering myeloid cells the only major source for leukotrienes. Dependent on the expression levels of LTA₄H and LTC₄S, myeloid cells produce LTB₄ or cys-LTs (Table 1) (1).

Leukotrienes bind to 7-transmembrane G protein coupled receptors. There are two such receptors for LTB₄: the high affinity receptor BLT1 and the low affinity receptor BLT2 (6–8). BLT1 is predominantly expressed on leucocytes (8–18), mediating chemotaxis and activation (Table 2) (15,19,20). Less is known about BLT2, which is ubiquitously expressed in humans and whose major ligand is 12(S)-hydroxy-5-cis-8,10-trans-heptadecatrienoic acid (12-HHT) rather than LTB₄ (3,21,22).

All cys-LTs bind to the receptors CysLT₁R and CysLT₂R (2). Recently, a third receptor for cys-LTs, CysLT₃R, has been identified, preferably binding LTE₄, the most abundant cys-LT, previously thought to play a negligible role due to its low affinity to CysLT₁R and CysLT₂R (23). Cys-LT receptors are widely expressed on hematopoietic and non-hematopoietic cells and mediate diverse effects (Table 2).

Expression of leukotrienes in inflammatory skin diseases

Leukotriene B₄ and LTC₄ levels in human skin are highly elevated under diverse inflammatory skin conditions, including AD, psoriasis, bullous pemphigoid and pemphigus vulgaris (24–29). Furthermore, also in a close correlate of human AD found in dogs, 5-LO expression is significantly upregulated in lesional skin (30).

In line with a major role of leukotrienes in the generation of skin inflammation, exogenous leukotrienes exert strong proinflammatory effects on healthy human skin. For example, LTB₄ applied epicutaneously onto human skin elicits a wheal and flare reaction accompanied by the formation of epidermal neutrophil

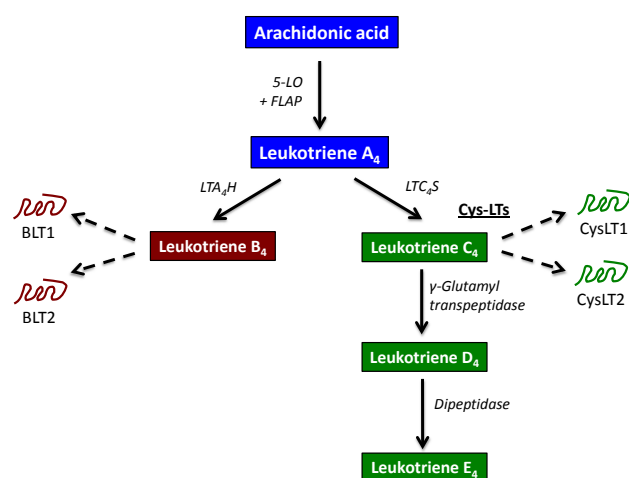


Figure 1. Biosynthesis of Leukotrienes. Arachidonic acid serves as common substrate in the biosynthesis of all leukotrienes. Arachidonic acid is first converted to leukotriene A₄ (LTA₄) by 5-lipoxygenase (5-LO), which requires association with the scaffold protein FLAP. LTA₄ is the last common precursor of all leukotrienes. Conversion of LTA₄ by LTA₄ hydrolase (LTA₄H) yields leukotriene B₄ (LTB₄). LTB₄ binds to the receptors BLT1 and BLT2. Alternatively, LTA₄ can be conjugated with reduced glutathione in a reaction catalysed by LTC₄ synthase (LTC₄S) to yield leukotriene C₄ (LTC₄). Successive hydrolysis of the glutathionyl moiety of LTC₄ yields leukotriene D₄ (LTD₄) and leukotriene E₄ (LTE₄). LTC₄, LTD₄ and LTE₄ are commonly referred to as cysteinyl leukotriene (cys-LTs). All cys-LTs bind to the receptors CysLT1 and CysLT2. Notably, additional receptors for cys-LTs have recently been identified.

Table 1. Relative capacity of leukocyte lineages to produce LTB₄ and cys-LTs

Leukocyte type	LTB ₄	cys-LTs
Neutrophils	Strong	None
Eosinophils	None	Strong
Basophils	None	Strong
Monocytes/Macrophages	Medium	Medium
Mast cells	Weak	Strong
Dendritic cells	Medium	Weak
Lymphocytes	None	None

Table 2. Select effects of LTB₄ and cys-LTs on specific cell types and tissues, respectively

Cells or tissue	LTB ₄	cys-LTs
Leukocytes	Chemoattraction (primarily neutrophils, macrophages, and T cells), CD11b upregulation, ROS and protease release	Chemoattraction (primarily eosinophils and mast cells), induction of T _H 2 cytokines
Endothelium	Leukocyte adhesion	Vasopermeability
Fibroblasts	Proliferation, migration (synovium)	Collagen production (skin and lung)
Smooth muscle cells	Migration (vascular cells), contraction (indirectly in blood vessels)	Contraction (respiratory tract) Concentration dependent contraction or relaxation (blood vessels)
Bone	Enhanced osteoclast activity	Osteoclast formation

microabscesses (31). Similarly, application of cys-LTs to human skin enhances vasopermeability and induces vasodilation followed by a wheal and flare reaction (32), which may be responsible for the development of urticaria after IgE-mediated skin mast cell activation (33).

A dual role for leukotrienes in the orchestration of allergic skin inflammation

Recently, evidence for a pivotal role of LTB₄ in the pathogenesis of AD was provided by Oyoshi et al. (34), using a model of allergic skin inflammation reflecting major features of AD (35). The authors showed that LTB₄ and its receptor BLT1 are both required for the recruitment of neutrophils into the skin in response to skin scratching. Herein, tape stripping of human or shaven murine skin, inflicting microinjuries to the epidermis, served as surrogate for microinjuries caused by scratching. While unstripped human and murine skin each were devoid of neutrophils and only showed negligible basal levels of LTB₄, tape stripping caused enhanced LTB₄ levels within the skin and sparked marked recruitment of neutrophils into the skin.

Additionally, in both species, tape stripping initiated pronounced epidermal-dermal thickening. Kinetics conducted in tape-stripped murine skin revealed that neutrophil infiltration peaked after 24 h and had almost vanished after 72 h. Furthermore, depletion of neutrophils reversed the tape stripping-induced increase in LTB₄ skin levels, while deficiency in mast cells had no impact on LTB₄ levels, suggesting that neutrophils are the major source of LTB₄ (Fig. 2).

Further examination of BLT1-deficient (*Ltb4r1*^{-/-}) and LTA₄ hydrolase-deficient (*Lta4h*^{-/-}) mice revealed that neutrophil recruitment into tape-stripped skin was predominantly directed by LTB₄ and mediated *via* its receptor BLT1, with neutrophil infiltration into tape-stripped skin strongly decreased in both gene-deficient strains as well as under pharmacological inhibition of LTA₄H.

Elegant adoptive transfer experiments of wild-type, *Ltb4r1*^{-/-} or *Lta4h*^{-/-} neutrophils into neutrophil-depleted mice further suggested that autocrine and paracrine actions of LTB₄ on neutrophils are crucial for the recruitment of neutrophils into tape-stripped skin and proved the concept that under some conditions neutrophils act as pivotal regulators of their own recruitment into the skin. This manner of self-regulation of early neutrophil recruitment into the skin is reminiscent of recent findings made in autoantibody-induced arthritis, a neutrophil-driven mouse model of inflammatory arthritis similarly dependent on LTB₄ and BLT1 both expressed by neutrophils (18,36–38). Furthermore, it is in line with the recent finding of LTB₄ as the critical mediator instigating ‘swarm-like’ behaviour of neutrophils, that is, the rapid migration of high numbers of neutrophils to inflammatory foci in a closed formation within peripheral tissues (39).

Notably, skin scratching was suggested to precipitate skin lesions in AD patients (40), and LTB₄ is an important mediator that induces the sensation of itching in mice (41,42). Hence, a vicious circle of scratching → neutrophil recruitment → LTB₄ release → increased itching → scratching conceivably drives AD.

To reflect the situation in the skin of AD patients in more detail, Oyoshi et al. sensitized mice against ovalbumin (OVA) by epicutaneous application of OVA on the shaved and tape-stripped back skin three times a week over a period of 7 weeks. This treatment induced allergic skin inflammation in wild-type mice characterized by infiltration of the skin dominated by CD4⁺ T cells and eosinophils. In line with the observations made in tape-stripped skin, *Ltb4r1*^{-/-} mice were protected from allergic skin

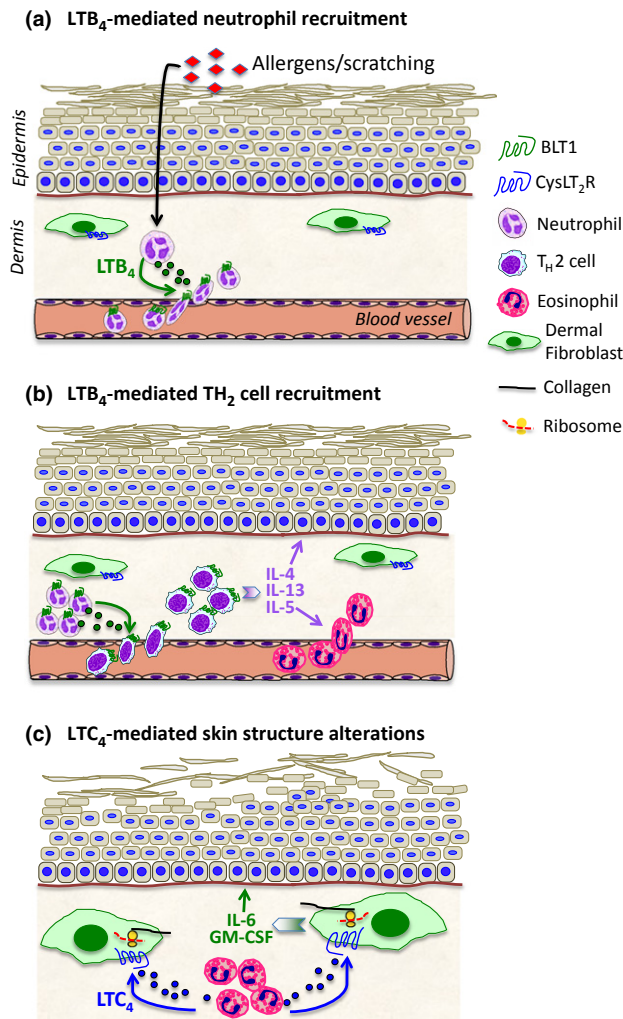


Figure 2. The pivotal roles of leukotrienes in the pathogenesis of allergic skin inflammation. Leukotrienes are believed to play a pivotal role both in the recruitment of effector cells in the skin in the initiation of allergic skin inflammation and in the development of consequent structural alterations of the skin. (a) Allergen exposure combined with scratching of the skin initiates the recruitment of neutrophils into the dermis. This recruitment is directed by neutrophil-derived LTB_4 . (b) In the next step, neutrophil-derived LTB_4 is also responsible for the recruitment of T_H2 cells into the skin. The release of T_H2 cytokines regulates the recruitment of eosinophils into the dermis. (c) In the dermis, eosinophils release LTC_4 , which binds to CysLT₂R on dermal fibroblasts, activating these cells to produce collagen as well as to release IL-6 and GM-CSF. These two processes cause dermal fibrosis and local keratinocyte hyperproliferation, two major skin alterations typically found in chronic allergic skin inflammation.

inflammation induced by epicutaneous sensitization. Unlike wild-type mice, *Ltb4r1*^{-/-} mice did not exhibit significant recruitment of CD4⁺ T cells and eosinophils into OVA-challenged skin.

Addressing the role of BLT1 on CD4⁺ T cells, an adoptive transfer model was conducted, in which allergic skin inflammation is transferred from a sensitized mouse to a non-sensitized mouse by transfer of OVA-stimulated CD4⁺ splenocytes from the former to the latter mouse. Transferring inflammation failed when *Ltb4r1*^{-/-} CD4⁺ splenocytes were transferred into a wild-type mouse, indicating that BLT1 on CD4⁺ T cells is indispensable to initiate allergic skin inflammation. Intriguingly, the converse

transfer of wild-type splenocytes into *Ltb4r1*^{-/-} mice also could not transfer inflammation, suggesting that BLT1 is required on at least one cell type in addition to CD4⁺ T cells.

To test whether neutrophils may be this additional cell type, wild-type neutrophils and CD4⁺ T cells were jointly adoptively transferred into *Ltb4r1*^{-/-} mice, which induced allergic skin inflammation in *Ltb4r1*^{-/-} mice. Joint transfer of wild-type CD4⁺ T cells with *Ltb4r1*^{-/-} neutrophils into *Ltb4r1*^{-/-} mice, however, did not elicit allergic skin inflammation. Hence, BLT1 on both neutrophils and CD4⁺ T cells is required to initiate allergic skin inflammation, suggesting a pivotal LTB_4 -driven neutrophil – T cell axis in the generation of allergic skin inflammation (Fig. 2). Further investigations showed that neutrophils in the skin direct CD4⁺ T cells into the skin by releasing LTB_4 .

These findings exemplify that neutrophils are more than mere effector cells but choreographers of inflammation. In addition to amplifying their own recruitment into inflammatory foci, as previously suggested (38), these new findings indicate that they can also control the recruitment of other immune cell types, including cells of the adaptive immune system, into peripheral tissues.

Likewise, the role of LTC_4 in AD has recently been addressed by means of the epicutaneous sensitization model (43). In contrast to LTB_4 , LTC_4 was not required to direct immune cell recruitment into the skin, but was a major regulator of skin structure alterations, precisely skin thickening and collagen deposition resulting in dermal papillary fibrosis and epidermal hyperplasia (Fig. 2), both hallmarks of chronic AD (44,45). While neutrophils were the essential source for LTB_4 in this model, LTC_4 release completely depended on eosinophils, which are plentiful in AD and inflammatory fibrotic tissue lesions (46).

Eosinophil recruitment in allergic skin inflammation largely depends on the chemokine receptor CCR3 on eosinophils, whose ligands CCL11/eotaxin, CCL24/eotaxin-2, CCL7/MCP-3 and CCL5/RANTES are highly expressed in both inflamed murine skin and in human AD lesions (47,48). The expression of eosinophil-active chemokines in the skin is primarily regulated by the T_H2 cytokines IL-4 and IL-13, which are abundantly expressed in the skin after BLT1-mediated T_H2 cell recruitment (34). Additionally, a CCR8⁺ T_H2 cell subtype enriched in IL-5 is recruited to the skin (48,49). IL-5 primes eosinophils to respond to chemoattractants, including CCR3 ligands and LTB_4 , and prolongs their survival in peripheral tissue, thus promoting allergic inflammation (50,51).

Consistent with the critical role of eosinophil-derived cys-LTs in allergic skin inflammation, both Δ dblGATA eosinophil-deficient and LTC_4 synthase-deficient mice were completely protected from skin thickening and collagen deposition, which are residual tissue alterations in the wake of allergic skin inflammation. Although protected from these residual tissue alterations, Δ dblGATA eosinophil-deficient and LTC_4 synthase-deficient mice both exhibited acute allergic inflammation with infiltration of sensitized skin by CD4⁺ T cells and elevated levels of IL-4 and IL-13 expression in the skin as well as of elevated OVA-specific IgE and IgG serum levels, showing that eosinophils and LTC_4 are not required for acute inflammation.

Skin thickening and collagen deposition reappeared when Δ dblGATA mice were reconstituted with wild-type eosinophils, but not when reconstituted with LTC_4 S-deficient eosinophils. Skin fibrotic effects were exclusively mediated *via* CysLT₂R. Thus,

CysLT₁R-deficient mice were fully susceptible to skin thickening and collagen deposition in allergic skin inflammation, whereas CysLT₂R-deficient mice were fully resistant. Mechanistically, the increase in CysLT₂R mediated collagen production occurred by LTC₄ directly activating collagen production in dermal fibroblasts. Additionally, LTC₄ induced the release of IL-6 and GM-CSF from dermal fibroblasts. Both cytokines promote keratinocyte proliferation, which is another characteristic feature of AD skin lesions (52,53).

Another role of cys-LTs in allergic inflammation has recently been highlighted in a mouse model of allergic pulmonary inflammation. In this model, both biosynthesis of cys-LTs by dendritic cells (DCs) and activation of CysLT₁R on dendritic cells were required to elicit full-blown allergic pulmonary inflammation either induced by direct sensitization and challenge with extracts of the house dust mite species *Dermatophagoides farina* (Df) or by adoptive transfer of Df-pulsed DCs (54). This requirement was reflected by significantly reduced numbers of eosinophils and T_H2 cells in the inflamed lungs of LTC₄S- and CysLT₁R-deficient mice directly sensitized to Df or in wild-type mice adoptively transferred with Df-pulsed LTC₄S- or CysLT₁R-deficient DCs, indicating that autocrine effects of cys-LTs via CysLT₁R on DCs participate in mounting T_H2 immune responses. Intriguingly, at the same time, CysLT₂R on DCs, conversely, counteracted allergic pulmonary inflammation (55), indicating an intricate regulatory network constituted by cys-LTs and their receptors controlling DC activity. In allergic skin inflammation to OVA, on the other hand, cys-LTs were not critical for sensitization (43). At this point, it remains elusive if these distinct roles of cys-LTs in allergic pulmonary and allergic skin inflammation reflect organ-specific or rather allergen-specific differences of the mechanisms in the sensitization phase of T_H2 allergies.

Conclusions

In recent years, new intriguing results have been obtained from mouse models indicating a requirement for leukotrienes in the pathogenesis of atopic dermatitis. Herein, both LTB₄ and cys-LTs play pivotal roles, but they act independently and in distinct stages of disease, with LTB₄ choreographing skin inflammation and cys-LTs subsequently regulating skin fibrosis, a major sequela of

allergic skin inflammation. These findings nicely illustrate how LTB₄ and cys-LTs sequentially work in concert to promote T_H2-driven allergic inflammation.

The role of leukotrienes in T_H1-driven allergic skin inflammation is less clear. LTB₄/BLT1, however, may also play an important role in the initiation of these diseases. Thus, also in a mouse model of delayed-type hypersensitivity, *Ltb4r1*^{-/-} mice were partially protected from disease (56).

The pivotal role of leukotrienes in mouse models of AD is now well established. The role of leukotrienes in AD in humans, however, is still elusive. As leukotrienes are highly expressed in human AD lesions, a significant contribution of leukotrienes to the human AD is possible, but data on the effect of leukotriene inhibition on the course of AD are scarce. In a pilot study applying zileuton, a 5-LO inhibitor, to six patients with severe AD, all individuals showed significant improvement of disease (57). Other small studies testing the effect of CysLT₁R inhibitors showed mixed results (58–60). Notably, the latest results from mouse models summarized in this *Viewpoint* article do not provide a rationale for using CysLT₁R inhibitors in AD patients, but rather CysLT₂R inhibitors. Notably, the first selective CysLT₂R inhibitor has recently been described, providing the opportunity to examine CysLT₂R inhibition in AD patients (61). Therefore, larger future clinical trials are still to clarify whether leukotrienes participate in the pathogenesis of AD in humans and whether they constitute valuable pharmacological targets for AD treatment.

Despite a wealth of data showing increased leukotriene expression in various inflammatory skin diseases, the mouse model of allergic skin inflammation is the first model of a specific inflammatory skin disease in which the role of leukotrienes has been addressed. The development of new, sophisticated mouse models for inflammatory skin diseases, such as blistering autoimmune diseases and psoriasis, in recent years has provided the research tools to address the role of leukotrienes in the next years in more detail (62–64).

Author Contribution

C.D.S., T.S., N.D.K. wrote the paper.

Conflict of interests

The authors have declared no conflicting interests.

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