



Potential Role of Endothelin-1 in Atopic Dermatitis

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Abstract

Purpose of review Atopic dermatitis (AD) is a chronic eczematous skin disease associated with intense pruritus and skin barrier dysfunction. Not only histamine, but also various pruritogens can induce itch in the skin of AD patients. Among them, one of the potentially endogenous pruritogens in the skin is endothelin-1 (ET-1). To understand the mechanism of action, production, and roles of ET-1 in the skin of AD, we reviewed recent advances in the understanding of ET-1.

Recent findings Recently, functions of ET-1 related to inflammation other than itch have been reported. The expression of ET-1 and IL-25 was found to be coordinately upregulated in the lesional skin of AD patients and a murine AD model. IL-25 augmented ET-1 expression, and ET-1 reciprocally increased IL-25 expression in keratinocytes. In addition, ET-1 directly induced phenotypic and functional maturation of murine bone marrow-derived dendritic cells (DCs) and modified T cell responses.

Summary ET-1 might be involved not only in pruritus but also in inflammation of AD. ET-1 may be a future target for antipruritic and anti-inflammatory agents in AD treatment.

Introduction: itch in atopic dermatitis

Atopic dermatitis (AD) is characterized by chronic eczematous inflammation, skin barrier dysfunction, and intense pruritus [1, 2]. Intense pruritus (itch) is the most burdensome symptom and the main chief complaint of AD patients [1–3]. Itch is a specialized perception of the skin and an unpleasant sensation that elicits the desire to scratch in order to remove noxious stimuli, leading to scratching behavior [4, 5]. Itch-induced scratching appears to aggravate preexisting skin inflammation in AD [5, 6]. In addition, itch and scratching cause sleep loss and severely disturb the quality of life and productivity of AD patients [7–9].

In general, itch is mediated by unmyelinated C-fiber afferents and thinly myelinated A δ -fiber afferents, and these cutaneous sensory nerve fibers originate from cell bodies in the dorsal root ganglion (DRG) [5, 10, 11]. The free nerve endings existing in the epidermis, papillary dermis, and around skin appendages are activated by endogenous and exogenous pruritogens through relevant receptors. At least two types of pruriceptive neurons, namely, histamine-dependent and histamine-independent afferents, have been identified in the murine DRG with substantial overlap. These two systems appear to exist separately and independently from one another, although they are closely related [5, 12, 13]. The best studied pruritogen is histamine, which is typically released from mast cells and basophils in the context of a type I hypersensitivity reaction [4, 5, 13]. Histamine activates a subset of sensory neurons that express histamine H₁ receptor (H₁R) and H₄R.

However, antipruritic effects of antihistamines are limited in the treatment of AD [3–5, 13]. This clinical observation implies that itch in AD patients is induced mainly by the non-histaminergic pathway.

Various pruritogens and their specific receptors stimulate itch signaling in the skin of AD patients. In particular, pruritogens related to inflammation have recently attracted attention. For example, endogenous and exogenous pruritogens produced from keratinocytes or immune cells are involved in such stimulation, including histamine; interleukin-31 (IL-31), IL-4, IL-13, and IL-33; thymic stromal lymphopoietin (TSLP); and endothelin-1 (ET-1) (Table 1) [14–21, 22••, 23]. In AD, epidermal barrier disruption promotes inflammation through dysregulation of immunomodulatory proteins and the release of damage-associated molecular-pattern molecules, including alarmins such as IL-33 and TSLP. The release of IL-33 and TSLP initiates Th2-cell-mediated responses, and Th2 cells release IL-4, IL-13, and IL-31 [2, 13]. Interestingly, these keratinocyte-derived mediators (TSLP and IL-33) or Th2-related inflammatory cytokines (IL-4, IL-13, and IL-31) can directly activate itch sensory neurons [16, 17, 19] and control both cutaneous inflammation and itch at the same time. In other words, itch and cutaneous inflammation are not independent, but are likely to be controlled at the same time by several key factors. One endogenous mediator that has been implicated in itch is ET-1 [22••, 23]. Recently, the involvement of ET-1 in cutaneous inflammation and immune responses has gradually been elucidated [22••, 24••].

The functions of ET-1: ET-1 induces itch

ET-1 is a 21-amino-acid peptide and is expressed by a variety of cell types, including endothelial cells, neurons, immune cells, and keratinocytes [22••, 25–27]. ET-1 was found to be a potent vasoconstrictor and is upregulated in response to hypoxia, stress, and a range of inflammatory cytokines [28–31]. The biological effects of ET-1 are mediated through the activation of endothelin A receptor (ET_AR) and endothelin B receptor (ET_BR). Besides its vasoconstrictive properties, ET-1 is also involved in cell signaling and inflammatory processes [32–34], and increased ET-1 expression is closely associated with a number of diseases, such as scleroderma, psoriasis, and asthma [35–38]. In addition to its systemic functions, ET-1 exerts important functions locally at the skin level, such as increasing keratinocyte proliferation, neo-angiogenesis, and leukocyte

Table 1. Pruritogens produced from keratinocytes or immune cells

Pruritogen	Receptor	Source
TSLP	TSLPR/IL-7R α	Keratinocyte
IL-33	ST2/IL-1RAP	Keratinocyte
IL-4	IL-4R α /IL-2R γ	Th2 cell, basophil, mast cell, innate lymphoid cell 2
IL-13	IL-4R α /IL-13R α_1	Th2 cell, innate lymphoid cell 2
IL-31	IL-31R α /OsmR	Th2 cell
ET-1	ET _A R	Keratinocyte
Histamine	H _{1/4} R	Mast cell, basophil

TSLP, thymic stromal lymphopoietin; IL-1RAP, IL-1 receptor accessory protein; *OsmR*, oncostatin M receptor; ET_AR, endothelin A receptor

chemotaxis, which are among the main characteristics of inflammatory skin disease [27, 39]. ET-1 levels were actually found to be increased in sera or lesional skin of psoriatic patients, compared with those in normal subjects [37]. These findings indicate that ET-1 may be involved in inflammatory processes associated with psoriasis. In addition, a number of studies have suggested that ET-1 has a role in itch, which is a major diagnostic criterion of AD and one of its most troublesome symptoms, as described above. It has been reported that ET-1 induces pruritus in rats and mice [40–45] as well as humans [23, 46, 47] by a histamine-independent mechanism. Intradermal (i.d.) injection of ET-1 in humans was reported to elicit burning itch [23, 46, 47] or pain sometimes accompanied by itch [48]. Moreover, also in humans, ET-1 induced a brief pain sensation and prolonged itch that was only partially and weakly inhibited by an antihistamine [23], and ET-1 was shown to be upregulated in patients with chronic itch due to prurigo nodularis [23] or AD [22••, 24••], suggesting a role for ET-1 in chronic itch. The i.d. injection of ET-1 elicited scratching behavior in rats and mice [40–45]. Moreover, i.d. microinjection of ET-1 in the cheek of mice elicited hindlimb scratching (indicative of itch) as well as forelimb wiping responses (indicative of pain) [49, 50], suggesting that ET-1 elicits both itch and pain sensations. The pruritogenic effect of ET-1 in rodents is mediated in large part by ET_AR, although the expression of ET_BR has been detected in satellite glial cells and non-myelinated Schwann cells of DRG [5, 44].

AD and ET-1

The effects of ET-1 on keratinocytes (Fig. 1)

Keratinocytes can produce cytokines and growth factors, some of which can stimulate cell proliferation through an autocrine loop. It was reported that ET-1 is produced in keratinocytes and acts through the ET_A receptor as an autocrine growth factor for these cells [51].

IL-25 was first described as a Th2-cell-derived cytokine and was found to be expressed in keratinocytes [52]. Recently, keratinocyte-derived IL-25 has been identified as one of the initiators of Th2 responses [53]. In a study to reveal the relationship between ET-1 and IL-25, the expression of ET-1 and IL-25 was coordinately upregulated in the lesional keratinocytes of patients with AD and a murine AD model [22••]. These findings suggested the possibility that ET-1 and

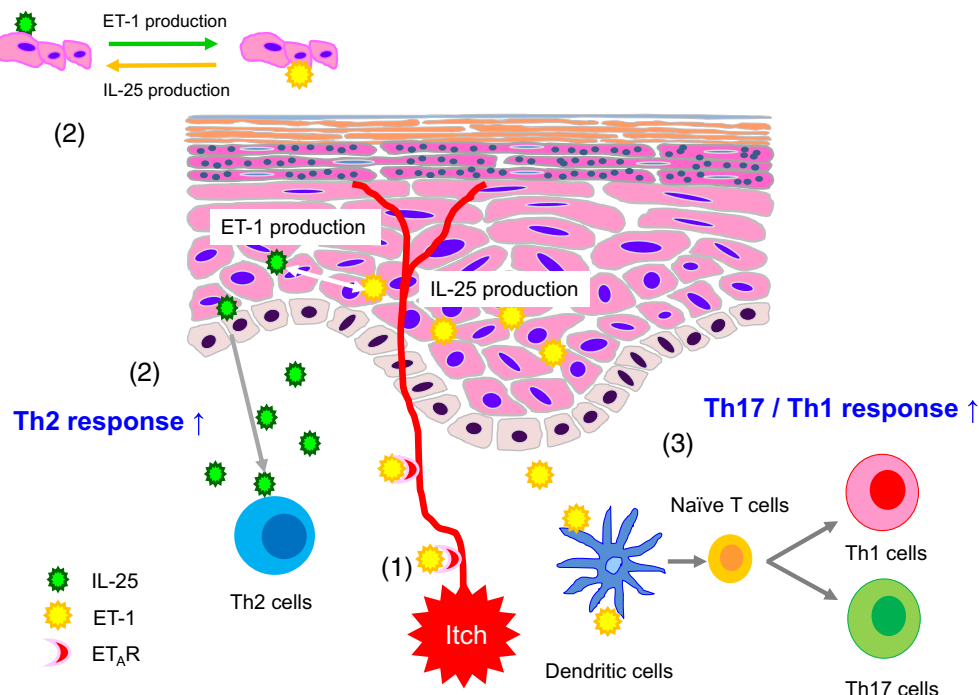


Fig. 1. The possible roles of endothelin-1 (ET-1) in the pathogenesis of atopic dermatitis. (1) ET-1 induces itch through endothelin A receptor (ET_AR). (2) The expression of ET-1 is upregulated in the lesional keratinocytes of atopic dermatitis (AD). IL-25 augmented ET-1 expression in keratinocytes, and ET-1 reciprocally increased IL-25 expression in keratinocytes. ET-1 is thought to be potentially involved in the inflammatory process of AD by augmenting the production of IL-25, which accelerates Th2 immune deviation. (3) ET-1 directly induces phenotypic and functional maturation of dendritic cells (DCs). ET-1-activated DCs primed T cells to produce Th1 and Th17 cytokines. The overexpression of epidermal ET-1 might be related to the chronicity of AD or some AD subtypes.

IL-25 interact with each other in the lesional skin of AD. In fact, IL-25 augmented ET-1 expression in keratinocytes through ERK1/2 and JNK signaling pathways, and ET-1 reciprocally increased IL-25 expression in keratinocytes through ET_AR via ERK1/2 and p38 MAPK signaling pathways [22••]. This vicious circle of mutual positive feedback between ET-1 and IL-25 may be part of the pathogenesis of AD. ET-1 is thought to be potentially involved in the inflammatory process of AD by augmenting the production of IL-25, which accelerates Th2 immune deviation.

The effects of ET-1 on the functions of dendritic cells (Fig. 1)

Because AD is a T cell-mediated skin disease, the dynamics and functions of dendritic cells (DCs) have great impact on its pathogenesis. For example, TSLP induces the expression by DCs of OX40 ligand, which binds to the OX40L receptor on naïve T cells and stimulates Th2 differentiation [13]. Keratinocyte-derived IL-33 stimulates DCs and promotes type 2 immunity [54].

In a study that evaluated the direct effects of ET-1 on the functions of DCs, ET-1 directly induced phenotypic maturation of bone marrow-derived DCs

(BMDCs) [24••]. ET-1 upregulated the expression of MHC class II and the co-stimulatory molecule CD86, but not that of OX-40L, in BMDCs. In addition, ET-1 also induced robust TNF- α , IL-12p40, IL-12p70, and IL-23 production from BMDCs [24••]. ET-1-stimulated BMDCs showed a more potent allogeneic stimulatory capacity than BMDCs without ET-1 pretreatment, suggesting that the DC/T cell interaction is potentiated by ET-1 [24••]. Interestingly, ET-1-activated BMDCs primed T cells to produce Th1 and Th17 cytokines, but not Th2 cytokines [24••].

It has been reported that not only Th2 but also Th17 and Th1 cytokines are involved in the pathogenesis of AD, particularly during the chronic phase [55, 56]. In addition, several shared pathological and immunological features such as epidermal acanthosis and higher Th17 activation are frequently observed in the lesional skin of Asian AD and psoriasis [55, 57]. Moreover, in early AD lesions of infants, increased innate and IL-17-related inflammation is observed [55, 58]. Thus, the overexpression of epidermal ET-1 might be related to the chronicity of AD or some AD subtypes by modulating T cell cytokine production. It was also reported that higher expression of ET-1 in chronic lesions than in acute lesions was seen among AD patients, which strongly supports the concept. Depending on the partner of interaction, ET-1 may exhibit different functions in the pathogenesis of AD [22••, 24••]. ET-1 accelerates Th2 immune responses through the interaction of keratinocyte-derived IL-25. Meanwhile, ET-1 is associated with the Th17/1 response in terms of its relationship with DCs.

Plasma ET-1 levels in AD patients

In a study about the plasma ET-1 levels in AD patients, significant correlations of plasma ET-1 levels with the objective Severity Scoring of Atopic Dermatitis index, itch severity, and serum immunoglobulin E levels at the time of exacerbation were found [59]. During AD exacerbation, plasma ET-1 levels were elevated and were positively correlated with AD clinical severity, itch intensity, and serum IgE levels [59]. High levels of ET-1 have also been found in the serum of patients with psoriasis. ET-1 levels were increased in sera of psoriatic patients, compared with those in normal subjects [37]. In addition, there was a significant correlation between serum ET-1 values and Psoriasis Area and Severity Index scores [37]. Thus, ET-1 may be one of the factors involved in the features shared between AD and psoriasis.

Conclusions

AD is characterized by three cardinal features: type 2 immune response, skin barrier dysfunction, and chronic pruritus. However, gene expression analyses have revealed a broad spectrum of cytokine profiles attributable to Th1, Th17, and T22 cells in the skin of AD patients [55]. These findings indicate the contribution to some degree of multi-cytokine axes in the pathogenicity of AD. In addition to the induction of itch, ET-1 can induce Th2 response through the activation of keratinocytes and Th17/1 immune response through the

activation of DCs. Because ET-1 can control both pruritus and T cell-mediated immune responses, ET-1 may be a future target for antipruritic and anti-inflammatory agents in AD treatment.

Compliance with ethical standards

Conflict of interest

Takeshi Nakahara declares no conflict of interest. Makiko Kido-Nakahara declares no conflict of interest. Masutaka Furue declares no conflict of interest.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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