A review of the roles of keratinocyte-derived cytokines and chemokines in the pathogenesis of atopic dermatitis in humans and dogs

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Background – Dysfunction of the physical and chemical barriers of the skin may play roles in the pathogenesis of atopic dermatitis (AD) by facilitating penetration of antigens through the skin and consequently evoking aberrant immune reactions. It is now emerging that keratinocytes are actively involved in cutaneous immune reactions by producing various soluble factors initiated by inflammatory stimuli, including mechanical injury or activation of Toll-like receptors and protease-activated receptors. Among the soluble factors, keratinocyte-derived cytokines and chemokines skew Type 2 helper T (Th2) cell-dominant immune reactions, with the recruitment of Th2 cells.

Objective – To review the roles of keratinocyte-derived cytokines and chemokines in the pathogenesis of AD in humans and dogs.

Conclusion and clinical importance – Keratinocyte-derived cytokines such as thymus and activation-regulated chemokine, granulocyte-macrophage colony stimulating factor, thymic stromal lymphopoietin and interleukin-33 are involved in the pathogenesis of human AD and possibly in canine AD. These cytokines and chemokines may possibly be used as subjective clinical markers and therapeutic targets for both human and canine AD.

Introduction

Canine atopic dermatitis (cAD) shares many clinical characteristics with its counterpart in humans, such as the presence of genetic predisposition, the early age of onset, the predilection sites of the affected skin, the association of epidermal barrier defects, the frequent colonization by Staphylococcus spp. and the elevated serum Immunoglobulin E (IgE) against environmental allergens. Accumulated evidence suggests that cAD is generally considered to be a Type 2 helper T (Th2)-associated inflammatory disease, as well as human atopic dermatitis (AD). In human AD, keratinocytes have been shown to produce various soluble factors inducing Th2-associated inflammation in response to a variety of stimuli such as mechanical injury, allergens and bacteria. Thymic stromal lymphopoietin (TSLP) produced by keratinocytes acts as a master switch for the allergic inflammation by elicitng the differentiation of naïve T cells into Th2 cells via dendritic cells. Furthermore, keratinocytes enhance the production of Th2 cytokines including IL-5 and IL-13 from Th2 cells by producing IL-33. On the basis of these studies, keratinocyte-derived cytokines and chemokines are critical to skew the Th2 cell-dominant immune reaction with a recruitment of Th2 cells in the pathogenesis of AD. Therefore, findings focused on the biological immune function of keratinocytes may provide new paradigms for the treatment of both human and canine AD.

In this review, to understand the current concept on the role of keratinocyte-derived cytokines and chemokines in the immunopathogenesis of AD, we summarize studies describing human AD followed by the findings in cAD.

Filaggrin

Humans

The skin comprises three different structures, the epidermis, dermis and panniculus adiposus, and protects the body by providing a physical, chemical and immunological barrier. The stratum corneum, the outermost layer of the epidermis, is formed by corneocytes that have been derived from apoptosis of keratinocytes. Keratin and lipids in the stratum corneum play important roles in this first physical barrier. Keratin is bundled by filaggrin to form a dense protein–lipid matrix. It has been shown that skin barrier dysfunction due to mutations in filaggrin is a major pathogenic factor of human AD.

Dogs

In dogs with CAD, decreased ceramide content and abnormal stratum corneum ultrastructure suggest that skin barrier dysfunction is similar to that of humans with AD. Previous studies have indicated a possible association of filaggrin with skin barrier dysfunction in dogs.
with AD, however, direct evidence remains to be demonstrated.

**Tight junctions**

**Humans**

Tight junction proteins, such as claudins and occludins, regulate the attachment of keratinocytes and the transition of molecules by forming the second physical barrier. In humans with AD, expression of claudin-1 was shown to be reduced and inversely correlated with Th2 biomarkers. Furthermore, identification of claudin-1 SNPs revealed its association with AD in North American populations. These results suggest that impairments in tight junctions due to a reduction of claudin-1 contribute to dysfunction of the second physical barrier in humans with AD.

**Dogs**

In an experimental cAD model, it was shown that the expression level of claudin-1 was reduced in nonlesional skin compared with normal skin. In another study of cAD, immunohistochemical analyses demonstrated decreased expression in zona occludens-1 and occludin, but not claudin-1. Although there have been no studies investigating the expression levels of proteins at tight junctions in naturally occurring cAD, previous results from experimental cAD models suggest that dysfunction of the second physical barrier may also exist in cAD, similar to human AD.

**Antimicrobial peptides**

**Humans**

Antimicrobial peptides derived from keratinocytes, such as cathelicidins, defensins and S100, play important roles in the chemical barrier function against various types of microorganisms. An immunohistochemical study demonstrated that expression of cathelicidins and beta-defensin-2 was decreased in both acute and chronic skin lesions of human AD compared with those in psoriasis. In the same study, however, there were no significant differences in the expression of cathelicidins and beta-defensin-2 between AD and healthy. A study using quantitative reverse transcription PCR (RT-qPCR) reported lower transcription levels of beta-defensin-2 in humans with AD compared with patients with psoriasis. The lower expression of antimicrobial peptides reported in these studies suggests that a deficiency in the expression of antimicrobial peptides may account for the susceptibility of skin infection by *Staphylococcus aureus* in humans with AD.

**Dogs**

Because recurrent staphylococcal skin infection or colonization is common in cAD, it is plausible that the reduced expression of antimicrobial peptides may also be involved in the pathogenesis of cAD. An initial study using RT-qPCR showed that transcription levels of beta-defensins-1, -2, -3 and cathelicidin in cAD were higher than those in healthy dogs. Another RT-qPCR study demonstrated that transcription levels of beta-defensins-1, -103 and -122 in skin lesions of cAD were lower than those in normal skin. However, in the same study, there were no differences in transcription levels of beta-defensin-1, -103 or -122 observed between cAD and other inflammatory skin diseases, suggesting that the reduced transcription may be attributed to inflammation, but does not predispose patients to bacterial colonization or infection. Finally, a similar study reported that no significant differences were found in the transcription levels of beta-defensin-1 and -103 in healthy, noninfected atopic or infected atopic skin. Interestingly, another study has reported significantly higher transcription of beta-defensin-103 in dogs with cAD than healthy dogs. Discrepancies in canine results suggest that further studies, such as immunohistochemical analyses, are necessary to clarify whether the role of antimicrobial peptides in cAD differs from that in human AD.

**Cutaneous immune reactions**

Dysfunction of the physical and chemical barriers in the skin facilitates skin penetration of antigens, evoking local immune reaction. In the skin, dendritic cells and keratinocytes are strongly associated with cutaneous immune reaction. Dendritic cells are antigen-presenting cells that activate T cells, several types of which can be found in the skin, classified by the expression of specific surface molecules. It is known that dendritic cells in the skin play essential roles in polarizing helper T (Th) cells to either Type 1 helper T (Th1) or Type 2 helper T (Th2) cells. For polarizing the appropriate subset of Th cells, dendritic cells need to be activated by cytokines and chemokines derived from keratinocytes. Keratinocytes express various types of receptors to sense invading pathogens, which include Toll-like receptors (TLRs) and protease-activated receptors (PARs). Human keratinocytes express all TLRs except for TLR-7 and -8, indicating an ability to recognize constituents of microorganisms, such as bacterial lipopeptides, peptidoglycan and flagellin, lipopolysaccharides (LPS), single- and double-stranded RNA and unmethylated cytosine-phosphate-guanine (CpG) oligonucleotides of bacterial DNA. In dogs, canine keratinocyte progenitor cell line (CPEK) was shown to induce transcription of *tlr-1, tlr-2, tlr-4* and *tlr-6*. PARs belong to a subfamily of G protein-coupled, 7-transmembrane domain receptors, activated by specific proteolytic cleavage of their extracellular amino termini by proteases. Among PAR-1 to -5, PAR-2 has been shown to be expressed in the keratinocytes of humans, mice and dogs. Recent studies in humans and dogs have indicated that activation of TLRs and PAR-2 in keratinocytes induces the production of cytokines and chemokines necessary for initiating and maintaining allergic inflammation.

**Keratinocyte-derived cytokines and chemokines**

**Pro-inflammatory cytokines**

It has been known that keratinocytes produce a variety of cytokines; among them, pro-inflammatory cytokines,
such as IL-1, IL-6 and TNF, have been studied extensively in humans. Human keratinocytes produce both IL-1alpha and IL-1beta; however, only the active form of IL-1alpha can be detected in culture, attributed to the lack of IL-1 convertase that cleaves the IL-1beta precursor in keratinocytes. The biological activities of both IL-1alpha and IL-1beta are similar, including stimulation of acute-phase proteins, cytokine production, cellular adhesion, chemotaxis and T and B cell proliferation. Keratinocytes express the IL-1 receptor on their cell surface, and thus may respond to IL-1 in an autocrine manner. In dogs, neither the gene nor protein expression levels of IL-1 have been evaluated in keratinocytes.

IL-6 was shown to be expressed in keratinocytes of humans with psoriasis. Although IL-6 was first identified as a cytokine involved in the activation of lymphocytes, it has also been shown to be involved in vascular disease, lipid metabolism, insulin resistance, mitochondrial activities, the neuroendocrine system and neuropsychological behaviour. Together with TGF-beta, IL-6 is also known to be a potent inducer of Th1 differentiation from naïve T cells. IL-1beta and TNF are major activators of IL-6 expression, and other pathways, such as TLRs, prostaglandins, adipokines, stress responses and other cytokines, also promote IL-6 production. In cultured human keratinocytes, the expression of IL-6 receptor was observed in monolayer cells and the deeper cells of stratified keratinocytes, but not in the differentiated cells of the upper layers. In dogs, IL-6 transcription was reported to be increased in cultured primary keratinocytes stimulated with synthetic dsDNA.

TNF-alpha was shown to be produced by human keratinocytes stimulated with LPS or ultraviolet light. The main biological function of TNF-alpha is its cytotoxic effect by inducing apoptosis in tumour cells. TNF-alpha also mediates inflammation and immune response by inducing cytokine secretion by a variety of different cells. Human keratinocytes were shown to express TNF receptor 1, which is the main mediator of skin inflammation induced by TNF-alpha. Microarray analysis demonstrated that treatment of human keratinocytes with TNF-alpha induced transcription of genes associated with not only immune and inflammatory responses, but also with tissue remodelling, cell motility, cell cycle regulation and apoptosis, suggesting that TNF-alpha has a multifunctional effect on keratinocytes. In dogs, production of TNF-alpha was observed in keratinocytes stimulated with IFN-gamma and LPS. One study has reported that activation via PAR-2 increased the transcription of tnf-alpha in CPEK. TNF-alpha was also shown to induce transcription of CC chemokine ligand (CCL) 17 and CCL28 in CPEK, suggesting that canine keratinocytes likely express TNF receptor, similar to human keratinocytes.

Chemokines

Cellular trafficking is strictly regulated by interactions between chemokines and chemokine receptors. Accumulating evidence indicates that subsets of Th cells selectively express chemokine receptors, such as CXC chemokine receptor (CXCR) 3 in Th1, CC chemokine receptor (CCR) 4 in Th2 or CCR6 in Th17 cells. In dogs, such distinct subsets of Th cells have not been reported; however, one study has demonstrated that CCR4 was selectively expressed in canine Th2 cells. In both humans and dogs, atopic skin lesions in the acute phase are characterized by Th2 cell-dominant inflammation, suggesting that CCR4 plays a significant role in the trafficking of Th2 cells to lesional skin. Several studies in humans have demonstrated the infiltration of CCR4+ cells in the lesional skin of AD patients. In dogs, ccr4 was shown to be preferentially detected in lesional AD skin. In peripheral blood, the number of CCR4+ cells has been shown to be increased in both humans and dogs with AD. Thymus and activation-regulated chemokine (TARC/CCL17) and macrophage-derived chemokine (MDC/CCL20) are known to be biological ligands of CCR4. Keratinocytes were first identified as the major cellular source of TARC/CCL17 in the lesional skin of humans and dogs. Apart from TARC/CCL17, human keratinocytes produce a number of CC and CXC chemokines. The current understanding of the cytokine profile in AD lesions is that during the advancement toward the chronic state, T-cell subsets change from Th2 to a mix of Th1, Th2, Th17 and Th22, suggesting that a more complex chemokine network may be involved in the pathogenesis of AD.
 major allergens and a cysteine protease.93 Similar to Der f
likely mediated via PAR-2 by Der f 1, which is one of the
protease inhibitor, suggesting that its production was most
production was suppressed by addition of a cysteine pro-
tein to cell culture medium.94 These results suggest that
GM-CSF production in CPEK activated via PAR-2
by antigen peptides increased the transcription level of
tarc/ccl17.40 Thus, exogenous proteases from mite allergens
may directly induce TARC/CCL17 production in ker-
atinocytes via PAR-2. Numerous clinical studies in
humans have demonstrated that plasma or serum TARC/
CCL17 level is correlated with disease severity, and has been
used as a useful biomarker in AD.76,80–84 At present, a
clinical study of plasma and serum TARC/CCL17 levels
is ongoing in Japan to investigate its use as a potential
biomarker for cAD.

Granulocyte-macrophage colony-stimulating factor
(GM-CSF)
Granulocyte-macrophage colony-stimulating factor (GM-
CSF) is known classically as a pivotal cytokine able to
stimulate the proliferation of granulocytes and macro-
phages.85 GM-CSF is produced by various types of cells,
including activated T cells, B cells, NK cells, monocytes/
macrophages, endothelial cells, fibroblasts and epithelial
cells.86 Among the epithelial cells, keratinocytes are
included in the group of cells that not only produce GM-
CSF,87 but also express its receptor.88 The current under-
standing of GM-CSF is focused on its pro-inflammatory
functions in autoimmune and inflammatory diseases, par-
ticularly Th17 associated diseases.89 The association of
GM-CSF in the pathogenesis of AD has been investigated
in mice and humans.

In mice, GM-CSF inhibits IL-12 production in Langer-
hans cells, suggesting its important role in the induction
of the Th2-dominated immune responses in AD.90,91 In
humans, a greater number of gm-csf-transcribing cells were
detected by in situ hybridization in AD lesions.91 In
dogs, mRNA transcription and protein expression profiles
in cAD lesions are lacking. In vivo, production of GM-CSF
in keratinocytes of humans with AD was higher than that
of healthy controls.92 It was also shown that ker-
atinocytes from nonlesional skin of AD subjects exhibited
increased spontaneous and PMA-stimulated production
of GM-CSF.92 In dogs, CPEK were found to produce GM-
CSF upon stimulation by a house dust mite (HDM) aller-
gen, Dermatophagoides farinae (Der f).93 The GM-CSF
production was suppressed by addition of a cytokine pro-
tease inhibitor, suggesting that its production was most
likely mediated via PAR-2 by Der f 1, which is one of the
major allergens and a cytokine protease.93 Similar to Der f
1, papain, a naturally derived cytokine protease, also
induced GM-CSF production with translocation of nuclear
factor of activated T cells (NFAT) in CPEK, and production
was partially inhibited by cyclosporin.94 These results sug-
gest that GM-CSF production in CPEK activated via PAR-2
may be regulated not only by NFAT, but also by another
transcription factor, such as nuclear factor-kB (NF-kB) or
activator protein-1 (AP-1). A recent study demonstrated
that IL-17A, a typical Th17 cytokine, also induced the tran-
scription of gm-csf in CPEK.95 A number of clinical trials
targeting GM-CSF are underway in humans with rheuma-
toid arthritis, multiple sclerosis, asthma and plaque psori-
asis, but not AD.96

Thymic stromal lymphopoietin (TSLP)
Thymic stromal lymphopoietin (TSLP) was first identified
as a stimulator of B cell development in the culture super-
natant of a murine thymic stromal cell line.96 Northern
and RT-PCR analyses in various tissues revealed the tran-
scription of tsep in the spleen, thymus, kidney, lung and
bone marrow of normal mice.97 Following this, the human
orthologue was cloned and its transcription was detected
in the heart, liver, testis and prostate, with lower expres-
sion in the lung, skeletal muscle, kidney, spleen, ovary,
small intestine and colon, indicating a more widespread
tissue distribution pattern than murine tsep.98 To date, the
partial, but not full, length of canine tsep has been iso-
lated.99 The receptor of TSLP (TSLPR) was identified in
mice and humans, revealing a heterodimeric receptor that
consists of IL-7 receptor alpha-chain (IL-7R alpha) and
TSLPR alpha chain 1.100,101 To date, TSLPR has not been
cloned in dogs. The functional TSLPR is expressed mainly
in hematopoietic cells, liver, brain, skeletal muscle, kid-
ney, spleen and thymus.102

Among the haematopoietic cells with TSLP expression,
dendritic cells, CD4 and CD8 T cells, B cells, mast cells,
basophils, eosinophils and NK cells are capable of
responding to TSLP.103 TSLP is involved in a number of
biological functions, including maturation of dendritic
cells, expansion of T and B cells, and activation of innate
immune cells; it is associated with a growing number of
different disorders, including allergic inflammation, infec-
tion, cancer and autoimmunity.103 TSLP is associated
with the pathogenesis of human AD. Immunohistochemi-
al analyses with anti-TSLP monoclonal antibody demon-
strated high expression of TSLP in keratinocytes of the
uppermost layer of the epidermis in acute and chronic
AD.104 Another study indicated that the expression level
of TSLP in the stratum corneum was increased in AD
compared with healthy subjects, and was correlated with
dry skin score and stratum corneum hydration.105 TSLP
produced by keratinocytes activates CD11c+ dendritic
cells and induces production of TARC/CCL17 and MDC/
CCL22.104 Dendritic cells activated by TSLP-primed na
tive T cells produce Th2 cytokines, such as IL-4, IL-5 and IL-
13.104 In TSLPR−/− mice, allergic inflammation elicited by
epicutaneous immunization with ovalbumin was severely
attenuated, which was attributed to decreased infiltration
of eosinophils and decreased local expression of Th2
cytokines.106 Moreover, overexpression of skin-specific
TSLP induced skin lesions with an increasing number of
Th2 cells in the dermis, and elevated serum IgE levels.107
These results indicate that TSLP-stimulated dendritic cells
prime CD4 T cells with characteristic features of Th2
cells, leading to the development of skin lesions. Various
environmental and endogenous stimuli induce TSLP pro-
duction in the skin.108,109 TSLP production by mechanical
injury in mice has been suggested to be due to inflamma-
tory cytokines that were produced in the skin lesion.109 In
mice with a mutation in filaggrin, activation of PAR-2
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induced TSLP production in keratinocytes.\textsuperscript{108} Furthermore, AD-like skin lesion development by epicutaneous application of mite extracts was shown to be improved by a PAR-2 antagonist.\textsuperscript{108} Binding of TSLP to TSLPR in CD11c\textsuperscript{+} dendritic cells in humans was shown to activate multiple STAT proteins, such as STAT1, 3, 4 and 5, as well as JAKs 1 and 2.\textsuperscript{110} Although this signalling pathway in keratinocytes has yet to be elucidated, it is plausible that it is similar in both dendritic cells and keratinocytes.

In 2013, a partial canine \textit{tslp} cDNA was cloned and characterized. The predicted amino acid sequence deduced from the canine \textit{tslp} cDNA shares 60.8\% identity with human TSLP.\textsuperscript{98} Although the cDNA identified in the study was a partial transcript, the deduced amino acid sequence ended with a stop codon, suggesting that the partial cDNA encoded the signal peptide and mature sequence.\textsuperscript{98} It was later discovered that the human TSLP cDNA shares 60.8\% identity with human TSLP.\textsuperscript{99} Although the cDNA identified in the study was a partial transcript, the deduced amino acid sequence ended with a stop codon, suggesting that the partial cDNA encoded the signal peptide and mature sequence.\textsuperscript{99} Additionally, the canine TSLP gene locus codes for a soluble membrane growth stimulation expressed gene (ST2), which was originally discovered as an orphan receptor,\textsuperscript{123} and IL-1R accessory protein (IL-1RAcP).\textsuperscript{124} An alternative transcript from the ST2 gene locus codes for a soluble ST2 (sST2), which binds to and acts as a natural antagonist of IL-33.\textsuperscript{125} To date, the canine IL-33R complex has not been cloned. IL-33R is ubiquitously expressed not only in haematopoietic cells, including mast cells, basophils, eosinophils, Th2 cells, macrophages, dendritic cells, NK cells, NKT cells and type 2 innate lymphoid cells (ILC2), but also in structural cells, including endothelial cells, epithelial cells and fibroblasts.\textsuperscript{126} In particular, the expression of IL-33R was found to be high in Th2 cells,\textsuperscript{127} mast cells\textsuperscript{128} and ILC2.\textsuperscript{129} IL-33 induces the development of Th2-associated inflammation in asthma and AD by promoting the production of Th2 cytokines and survival of mast cells and eosinophils.\textsuperscript{130} Meanwhile, IL-33 has been shown to have various protective effects in helminth infections, attherosclerosis, obesity and type-2 diabetes.\textsuperscript{130} Genetic polymorphisms in the ST2 region have been associated with AD in humans.\textsuperscript{131} Furthermore, the transcription level of \textit{il-33} in lesional skin of human AD was shown to be higher compared with that in nonlesional skin.\textsuperscript{132} Immunohistochemical analyses revealed an increased expression of IL-33 in suprabasal keratinocytes and endothelial cells in human AD.\textsuperscript{133} Additionally, a number of IL-33R-expressing cells were observed in the dermis and epidermis of AD patients.\textsuperscript{133} IL-33 enhances the production of IL-5 and IL-13, but not IL-4, by Th2 cells,\textsuperscript{10} mast cells,\textsuperscript{128} and ILC2,\textsuperscript{129} whereas human basophils stimulated with IL-33 were shown to produce IL-4 as well as IL-5 and IL-13.\textsuperscript{134} In addition to Th2 cytokines, human mast cells stimulated with IL-33 were found to produce various cytokines and chemokines, including TNF-alpha, GM-CSF, IL-1beta, IL-3, IL-6, IL-10, CXC chemokine ligand (CXCL) 2, CXCL8, CCL1, CCL2, CCL3, CCL17, prostaglandin D2 and leukotriene B4.\textsuperscript{128,135}

The expression of TSLP in normal human epidermal keratinocytes (NHEKs) was upregulated by stimulation with IL-33 in a dose-dependent manner.\textsuperscript{136} It was demonstrated that the development of AD-like lesions in transgenic mice expressing IL-33 was driven by a keratin 14 promoter in keratinocytes.\textsuperscript{137} IL-33 can be released from keratinocytes by several factors, such as pro-inflammatory cytokines.
mechanical injury, allergens and bacteria. Stimulation with TNF-alpha and IFN-gamma upregulated expression of IL-33 in both HaCaT and cultured primary keratinocytes. Furthermore, upregulation of IL-33 was observed in human skin after tape stripping and in the skin of filaggrin-deficient mice, suggesting that barrier dysfunction leads to the expression of IL-33. In humans with AD, RT-qPCR analyses revealed the upregulation of IL-33 and ST2 in skin after patch testing with HDM and staphylococcal enterotoxin. Binding of IL-33 to the IL-33R complex recruited the adaptor molecule myeloid differentiation primary-response protein 88 (MyD88), IL-1R-associated kinase 1 (IRAK1) and IRAK4, consequently activating signalling pathways such as ERK, p38, JNK and NF-κB in mast cells and T cells. In keratinocytes, IL-33 induced the expression of TSLP through an early growth response protein 1 (Egr-1) dependent mechanism via ERK, JNK and p38.

A microarray analysis in acute cAD skin lesions revealed that the transcription of IL-33 was approximately three times higher than that in healthy dogs. Transcription analyses by microarray and RT-qPCR demonstrated the increased transcription of IL-33 in the skin of dogs sensitized to HDM allergens. These results suggest that canine IL-33 is likely involved in the pathogenesis of cAD, similar to human AD.

The potential benefits of an anti-IL-33 monoclonal antibody have been investigated in murine models of allergic diseases. Treatment with an anti-IL-33 monoclonal antibody inhibited allergen-induced eosinophilic airway inflammation, mucus hypersecretion and production of Th2-type cytokines in a murine asthma model. Administration of an anti-IL-33 antibody to an ovalbumin-induced allergic rhinitis model attenuated the frequency of nose scratching, serum IgE increases and eosinophil infiltration into airway tissues. In humans with AD, serum IL-33 levels were correlated with skin severity, suggesting its potential as a biomarker. These studies suggest that the IL-33/IL-33R pathway has potential as a therapeutic target and as a novel biomarker for AD.

Conclusion and future direction

Accumulated evidence demonstrates that keratinocyte-derived cytokines and chemokines, such as TARC/CCL17, GM-CSF, TSLP and IL-33, are involved in the pathogenesis of human AD and possibly in cAD. Thus, these cytokines and chemokines may possibly be used as subjective clinical markers and therapeutic targets for both human and canine AD. Therefore, prospective studies should focus more on the translation of such findings in fundamental research into dermatological practice.

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Résumé

Contexte – Le défaut des barrières physiques et chimiques de la peau peut jouer un rôle dans la pathogénie de la dermatite atopique (AD) en facilitant la pénétration des antigènes à travers la peau et par conséquence, entrainer des réactions immunes aberrantes. Il apparaît actuellement que les kératinocytes sont activement impliqués dans les réactions cutanées immunitaires en produisant des facteurs solubles variés initiés par les stimuli inflammatoires, comprenant des dommages mécaniques ou l’activation de TLR (Toll-like receptor) et PAR (protease-activated receptors). Parmi les facteurs solubles, les cytokines dérivées de kératinocytes et les chémokines dérivées de réactions immunitaires à dominante cellulaire de type Th2, avec le recrutement de cellules Th2.

Objectif – Revoir les rôles des cytokines et chémokines dérivées des kératinocytes dans la pathogénie de l’AD chez l’homme et le chien.

Conclusion et importance clinique – Les cytokines dérivées des kératinocytes telles que le thymus et les chémo kines d’action régulée, GMCSF (granuloctye-macrophage colony-stimulating factor), lymphopoietine stromale thymique et l’interleukine-33 sont impliquées dans la pathogénie de l’AD humaine et possiblement dans l’AD canine. Ces cytokines et chémokines pourraient être utilisées comme marqueurs cliniques subjectifs et cibles thérapeutiques à la fois pour l’AD canine et humaine.

Resumen

Introducción – las alteraciones de las barreras físicas y químicas de la piel pueden jugar un papel en la patogenia de la dermatitis atopica (AD) facilitando la penetración de antígenos a través de la piel y consecuentemente induciendo una reacción inmunitaria aberrante. Es cada vez más evidente que los queratinocitos están implicados activamente en las reacciones inmunitarias cutáneas produciendo varios factores solubles que inician en el estímulo inflamatorio, incluyendo daño mecánico o la activación de receptores tipo Toll y receptores activados por proteasas. Entre los factores solubles, las citokinas derivadas de queratinocitos y qumioquinas derivan las reacciones inmunitarias hacia una reacción dominada por linfocitos T2 adyuvantes (Th2), reclutando células Th2.

Objetivo – revisar el papel de las citoquinas derivadas de queratinocitos y las qumioquinas en la patogénesis de AD en humanos y perros.

Conclusión e importancia clínica – las citoquinas derivadas de queratinocitos tales como la qumioquina tímica y regulada por activación, el factor de estimulación de colonias de granulocitos-macrófagos, la linfopoietina tímica estromal y la interleuquina 33 están implicadas en la patogenia de la dermatitis atopica humana y posiblemente en la canina. Estas citoquinas y linfioquinas pueden ser utilizadas potencialmente como marcadores clínicos subjetivos y dianas terapéuticas tanto en humanos como en perros.

Zusammenfassung


Ziele – Eine Review der Rolle, die die aus den Keratinocyten stammenden Zytokine und Chemokine bei der Pathogenese der AD des Menschen und des Hundes spielen.


要約

背景 — 皮膚の生理学的、および化学的パリア機能不全は皮膚へのアレルゲンの浸透を促進し、その後の異常な免疫反応を引き起こすことにより、アトピー皮膚炎（AD）の病態に対する役割を果たしているかもしれない。機械的損傷あるいはToll様受容体の活性化およびプロテアーゼ活性化受容体を含む炎症性刺激に誘導された、様々な水溶性因子を産することによりケラチノサイトは皮膚免疫応答に積極的に関与していることが、近年明らかになった。水溶性因子の中で、ケラチノサイト由来サイトカインおよびデコマクシングがタイプ2ヘルパーT（Th2）細胞のリクルートメントとともにTh2細胞優位な免疫応答を変化させる。

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目的 — ヒトおよびイヌのADの病因における、ケラチノサイト由来サイトカインおよびケモカインの役割を概説することである。

結論および臨床的な重要性 — 胸腺および活性化制御ケモカイン、顔裂球—マクロファージコロニー刺激因子、胸腺間質性リンパ球新生因子ならびにインフラインシニ−33などのケラチノサイト由来のサイトカインがヒトADの病因に関与しており、イヌADでもその可能性がある。これらのサイトカインやケモカインはヒトとイヌADの両者において、主観的な臨床マークーカーおよび治療のターゲットとして利用できる可能性がある。

摘要
背景 — 皮肤物理と化学障害をもたらし、抗原刺激皮膚、それから引き起こす異常の免疫反応は異位性皮膚の病理学的な現象である。現実理論に、角質細胞を含む膿性細胞、如機械性障害やToll-like受容体と活性化蛋白を活性化する。可能性がある因子は、積極的に免疫応答を進行する。可溶性因子中、角質細胞を含む細胞因子、幹細胞を含む細胞因子、これら細胞を含む細胞因子を含む細胞因子は、ヒトおよび犬のADの原因として、その可能性がある。これらの細胞因子と幹細胞を含む細胞を受け入れることができる可能性がある。

総結和臨床意義 — 角質細胞を含む細胞因子、如機械性障害やToll-like受容体と活性化蛋白を活性化する。可能性がある因子は、積極的に免疫応答を進行する。可溶性因子中、角質細胞を含む細胞因子、幹細胞を含む細胞因子、これら細胞を含む細胞因子は、ヒトおよび犬のADの原因として、その可能性がある。これらの細胞因子と幹細胞を含む細胞を受け入れることができる可能性がある。

Resumo
Contexto — Disfunção da barreira física e química da pele pode participar da patogênese da dermatite atópica (DA) através da facilitação da penetração de antígenos pela pele e, consequentemente, evocar reações imunes aberrantes. Sabe-se, recentemente, que os queratinócitos estão envolvidos ativamente nas reações imunes cutâneas através da produção de diversos fatores solúveis incitados por estímulo inflamatório, incluindo trauma mecânico ou ativação de receptores Toll-like e de receptores ativados por proteases. Dentre esses fatores solúveis, citocinas e quimiocinas derivadas de queratinócitos estimulam reações imunes com predomínio de células T helper tipo 2 (Th2), recrutando células Th2.

Objetivo — Revisar o papel das citocinas e quimiocinas derivadas de queratinócitos na patogênese da DA em humanos e em cães.

Conclusão e importância clínica — Citocinas derivadas de queratinócitos como antigênicos regulados pelo timo e por ativação, fatores estimuladores de colônia de granulócitos-macrófagos, infopoeíntica do estroma tímico e a interleucina-33 estão envolvidas na patogênese da DA em humanos e, provavelmente, na DA canina. Estas citocinas e quimiocinas, possivelmente, podem vir a ser usadas como marcadores clínicos subjetivos e alvos terapêuticos tanto para DA humana quanto para canina.