Chemokines and Skin Diseases

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Abstract Chemokines are small molecules that induce chemotaxis and activation of certain subsets of leukocytes. The expression patterns of chemokines and chemokine receptors are specific to certain organs and cells. Therefore, chemokines are important to elucidate the mechanism of organ-specific human diseases. CCL17 expressed by Langerhans cells, blood endothelial cells, and fibroblasts plays a key role in attracting Th2 cells and tumor cells of adult T-cell leukemia/lymphoma and mycosis fungoides/Sézary syndrome into the skin, developing various Th2-type inflammatory skin diseases as well as cutaneous lymphoma. CCL11 and CCL26 expressed by skin-resident cells, such as fibroblasts, blood endothelial cells, and keratinocytes, induce infiltration of CCR3-expressing cells such as Th2 cells and eosinophils. CCL11 may also serve as an autocrine as well as a paracrine in anaplastic large cell lymphoma. CX3CL1 expressed on blood endothelial cells leads to infiltration of CX3CR1⁺ immune cells, such as mast cells, neutrophils, and macrophages, playing important roles in wound healing, tumor immunity, and vasculitis. Biologics targeting chemokines and their receptors are promising strategies for various skin diseases that are resistant to the current therapy.

Keywords CCL17 · CCR4 · CCL11 · CCL26 · CCR3 · CX3CL1

Abbreviations

AD	Atopic dermatitis
ALCL	Anaplastic large cell lymphoma
ATLL	Adult T-cell leukemia/lymphoma
CHS	Contact hypersensitivity
MF	Mycosis fungoides
SS	Sézary syndrome
Tg	Transgenic
WT	Wild-type

Introduction

Chemokines are small molecules that induce chemotaxis and activation of certain subsets of leukocytes. Most chemokines are 8–10 kDa in size, although CX3CL1 is around 90 kDa in its soluble form (Bazan et al. 1997). They are classified into four types: CC chemokines, CXC chemokines, C chemokines, and CX3C chemokine. The classification is based on the pattern of cysteine residues in each protein (Charo and Ransohoff 2006). Chemokines are promiscuous in their receptor binding. For example, CCL26 can bind CX3CR1 as well as CCR3 and thus may play a dual role in allergic disease, attracting eosinophils and T cells and monocytes (Nakayama et al. 2010). Accumulating evidence supports that chemokines have broader functions than just chemotaxis. The expression pattern of chemokines and chemokine receptors is specific to certain organs and cells. Therefore, chemokines are important to elucidate the mechanism of organ-specific human diseases. Many chemokines expressed in the skin, such as CXCL8, CXCL9, CXCL10, CCL11, CCL17, CCL26, and CCL27, mediate recruitment of leukocytes to the skin from the blood. There are also chemokines that mediate egress of leukocytes via the lymphatics such as

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CCL21, CXCL12, and CX3CL1. Both types of chemokines are important for maintaining skin homeostasis and their disruption can result in skin pathologies. The present review highlights roles of four chemokines that we have been studying these years: CCL17, CCL11, CCL26, and CX3CL1.

CCL17 and Skin Diseases

CCL17, also called thymus and activation-regulated chemokine, is a member of the CC chemokine family. It is a ligand of CCR4 and CCR8 and serves to recruit cells expressing these chemokine receptors (Inngjerdingen et al. 2000). CCL17 is mainly produced by dendritic cells (Imai et al. 1996; Sallusto et al. 1998b), fibroblasts (Yu et al. 2002), and blood endothelial cells (Campbell et al. 1999). Langerhans cells, skin-resident dendritic cells, produce high levels of CCL17 constitutively during culture even without exogenous stimuli. Stimulation with transforming growth factor (TGF)- β , tumor necrosis factor (TNF)- α , interleukin (IL)-4, IL-13 and anti-CD40 antibody enhanced the expression. In contrast, its production level decreased in the presence of granulocyte-macrophage colony-stimulating factor, interferon (IFN)- γ , or IL-10 (Fujita et al. 2005; Xiao et al. 2003). CCR4 is predominantly expressed on Th2 lymphocytes, basophils, and natural killer (NK) cells (Godiska et al. 1997; Nickel et al. 1999; Sallusto et al. 1998a).

CCL17-transgenic (Tg) mice which overexpress CCL17 in the epidermis showed enhanced Th2-type and decreased Th1-type contact hypersensitivity (CHS). An increased number of CCR4⁺ cells infiltrated in Tg mice. IL-4 mRNA expression level was higher and that of IFN- γ was lower in Tg mice in both acute and chronic CHS. Moreover, higher levels of serum IgE were observed in Tg mice after CHS (Tsunemi et al. 2006). Thus, interactions between CCL17 and CCR4 are important for skin inflammation by Th2-polarized cells. The importance of CCR4 in macrophages has also been shown using knockout mice. CCR4^{-/-} mice exhibited significantly decreased mortality on administration of high or low dose bacterial lipopolysaccharide compared with wild-type (WT) mice (Chvatchko et al. 2000). After high-dose lipopolysaccharide treatment, peritoneal lavage contained significantly smaller numbers of macrophages in CCR4^{-/-} mice. Intrapulmonary administration of bleomycin sulfate provoked lethal inflammatory and fibrotic responses in WT mice, while such responses were absent in CCR4^{-/-} mice (Trujillo et al. 2008). Transcript and protein analyses of alveolar and bone marrow-derived macrophages showed that cells isolated from CCR4^{-/-} mice did not exhibit CCL17-dependent M1 activation in response to bleomycin. CCR4^{-/-} mice were

similarly resistant to challenge with Toll-like receptor agonists as well as bacterial peritonitis (Ness et al. 2006). Macrophages from CCR4^{-/-} mice exhibited many features consistent with alternative activation. When the effects of CCR4 deficiency in oxazolone-induced CHS were examined, the inflammatory response in the skin at 24 h post-elicitation was stronger in CCR4^{-/-} mice compared to WT mice. There were enhanced ear swelling and increased inflammatory cell infiltration, probably due to deficient migration of suppressive T cells (Lehtimäki et al. 2010). Thus, interactions between CCL17 and CCR4 play critical roles in skin homing of Th2 cells, classical activation pathways of macrophages, and attraction of suppressive T cells into the skin.

CCL17 and CCR4 play important roles in the pathogenesis of inflammatory skin diseases such as atopic dermatitis (AD), bullous pemphigoid, dermatomyositis, papulopythroderma syndrome, and angioedema (Kawashima et al. 2010; Saeki and Tamaki 2006; Tamaki et al. 2006; Yokobayashi et al. 2008). Among them, AD showed variable and higher serum CCL17 levels than other skin diseases. In AD, serum CCL17 levels sharply reflected disease activity and decreased after the treatment in accordance with the improvement in clinical symptoms (Kakinuma et al. 2001). CCR4 expression levels on CD4⁺ peripheral blood mononuclear cells in AD patients were significantly higher than those seen in healthy controls (Wakugawa et al. 2001). Moreover, serum CCL17 levels are superior to those of other chemokines as a disease marker of AD (Kimura et al. 2014). Thus, CCL17 plays critical roles in various Th2-type skin diseases, especially in AD.

CCL17 is also important in hematological malignancy (Sugaya 2010). In patients with mycosis fungoides (MF) and Sézary syndrome (SS), both of which are cutaneous T-cell lymphoma, serum CCL17 levels were elevated, reflecting the disease activity (Kakinuma et al. 2003). We and others have shown that transformed large cells in tumor stage MF and SS express CCR4 (Ferenczi et al. 2002; Kakinuma et al. 2003; Sokolowska-Wojdylo et al. 2005; Yagi et al. 2006). Tumor cells of adult T-cell leukemia/lymphoma (ATLL) also express CCR4 (Yoshie et al. 2002). Mogamulizumab, a humanized defucosylated anti-CCR4 monoclonal antibody, showed potent antitumor activity mediated by highly enhanced antibody-dependent cellular cytotoxicity against primary ATLL cells both in vitro and ex vivo (Ishii et al. 2010). This drug demonstrated clinically meaningful antitumor activity in patients with relapsed ATLL with an acceptable toxicity profile (Ishida et al. 2012). It is now approved for use by the Japanese government in the treatment of recurrent ATLL and MF/SS. Taken together, CCL17 expressed by Langerhans cells, blood endothelial cells, and fibroblasts plays

Fig. 1 CCL17 expression by epidermal Langerhans cells, fibroblasts, and blood endothelial cells and infiltration of CCR4-expressing Th2 cells. CCR4 expression on ATLL/MF/SS tumor cells is important for their skin homing

a key role in attracting Th2 cells and tumor cells of ATLL and MF/SS into the skin, developing various Th2-type inflammatory skin diseases as well as cutaneous lymphoma (Fig. 1).

CCL11, CCL26, and Skin Diseases

CCL11 and CCL26 belong to the CC chemokine family. The former is also called eotaxin-1 and the latter is called eotaxin-3. Both of them have potent chemotactic activity for CCR3⁺ cells such as eosinophils (Forssmann et al. 1997) as well as subpopulations of Th2 cells (Sallusto et al. 1997). In cutaneous tissue components, CCL11 is produced by dermal fibroblasts (Bartels et al. 1996), blood endothelial cells (Rothenberg et al. 1995), and dendritic cells (Beaulieu et al. 2002). CCL26 is reported to be expressed by epidermal keratinocytes (Nishi et al. 2008), dermal fibroblasts (Hoeck and Woisetschlager 2001), and blood endothelial cells (Shinkai et al. 1999). CCR3, a receptor for CCL11 and CCL26, is expressed on eosinophils, basophils, and subpopulations of T cells (Forssmann et al. 1997; Sallusto et al. 1997; Ugucioni et al. 1997).

In vivo function of CCL11 and CCR3 has been studied using knockout mice. Eosinophils and the eosinophil product major basic protein were absent from the skin of ovalbumin-sensitized CCR3^{-/-} mice (Ma et al. 2002). Recruitment of eosinophils to lung parenchyma and bronchoalveolar lavage fluid was also severely impaired in CCR3^{-/-} mice, suggesting that CCR3 plays an essential role in eosinophil recruitment to the skin and the lung and in the development of airway hyperresponsiveness.

Analysis of airway eosinophilia revealed a dominant role for CCL24 and a synergistic reduction in CCL11/24 double-knockout mice as well as CCR3-knockout mice (Pope et al. 2005). Moreover, bleomycin-induced lung injury was significantly reduced in CCL11^{-/-} mice (Huaux et al. 2005). Expression of profibrotic cytokines such as TGF- β was diminished in the absence of CCL11, suggesting that CCL11 and CCR3 are important in the pulmonary recruitment of granulocytes and play significant pathogenic roles in lung fibrosis. Thus, interactions between CCL11 and CCR3 play important roles in skin and lung inflammation and fibrosis mainly mediated by eosinophils.

CCL11 protein is upregulated in a variety of inflammatory diseases that are characterized by massive infiltration of eosinophils, such as allergic asthma (Campbell et al. 1998; Ganzalo et al. 1996), allergic rhinitis (Baraniuk 1997), and AD (Kaburagi et al. 2001; Yawalkar et al. 1999), and is thought to be a key player in the pathogenesis of these conditions. CCL26 also plays important roles in allergic diseases such as AD and allergic asthma (Berkman et al. 2001; Kagami et al. 2003). Moreover, we and others reported association of CCL26 with angioedema (Yokobayashi et al. 2008), MF/SS (Miyagaki et al. 2010), bullous pemphigoid (Kagami et al. 2012), eosinophilic folliculitis (Nakahigashi et al. 2012; Yokobayashi et al. 2013), and eosinophilic cellulitis (Fujimura et al. 2014), all of which are regarded as Th2-type diseases.

Thus, both CCL11 and CCL26 play important roles in establishing Th2-dominant microenvironment in the skin.

There are emerging data suggesting that signaling through chemokine/chemokine receptor interactions is implicated with tumor growth and invasion of several

Fig. 2 CCL11/CCL26 expression by fibroblasts, blood endothelial cells, and keratinocytes and infiltration of CCR3-expressing cells such as Th2 cells and eosinophils. CCR3 expression on ALCL tumor cells is important for their proliferation

cancer types, including lymphomas, in an autocrine/paracrine manner. In most cases of anaplastic large cell lymphoma (ALCL), tumor cells express CCR3 (Kleinhans et al. 2003; Yamaguchi et al. 2006). ALCL cells also express CCL11 (Kleinhans et al. 2003). Therefore, CCL11 may act in autocrine manner in ALCL. Indeed, we demonstrated cell survival effects of CCL11–CCR3 interactions in ALCL cells (Miyagaki et al. 2011). CCL11 increased cell survival rates and promoted proliferation of CCR3⁺ lymphoma cells via extracellular signal-regulated kinase pathway. We also showed Bcl-xL and survivin expression in CCL11-stimulated lymphoma cells in vitro and ALCL tumor cells in situ. Taken together, CCL11 and CCL26 expressed by skin-resident cells such as fibroblasts, blood endothelial cells, and keratinocytes induce infiltration of CCR3-expressing cells such as Th2 cells and eosinophils (Fig. 2). CCL11 may serve as an autocrine as well as a paracrine in ALCL.

CX3CL1 and Skin Diseases

CX3CL1, also called fractalkine, and its receptor CX3CR1 have been identified as key mediators of transmigration of immune cells such as T cells, NK cells, and monocytes (Bazan et al. 1997; White and Greaves 2012). CX3CL1 is expressed by inflamed endothelial cells, epithelial cells, including keratinocytes, macrophages, and vascular smooth muscle cells, while CX3CR1 is mainly expressed on T cells, NK cells, neutrophils, monocytes, and mast cells (Imai et al. 1997; Sugaya et al. 2003; Yang et al. 2007). CX3CL1 exists in two forms, a membrane-bound and a soluble form, which

is an unusual feature of this chemokine. In its membrane-bound form, CX3CL1 acts as an adhesion molecule, whereas in its soluble form, it acts as a chemoattractant for T cells, NK cells, and monocytes (White and Greaves 2012). Monocytes can be classified into two functional subsets based on their chemokine receptor expression pattern: a short-lived CCR2⁺ subset that is actively recruited into inflamed tissues, and a CX3CR1⁺ subset characterized as residents within non-inflamed tissues (Geissmann et al. 2003). Ly6C⁺CCR2⁺CX3CR1[−] inflammatory and Ly6C[−]CCR2[−]CX3CR1⁺ resident monocytes are generally thought to differentiate into M1 and M2 macrophages, respectively. Recent studies have revealed that CX3CR1 is expressed on cells of the monocyte-macrophage dendritic cell lineage (Auffray et al. 2009; Jung et al. 2000) and that CX3CL1 promotes trafficking of dendritic cells through inflamed lymphatics (Johnson and Jackson 2013).

CX3CR1^{−/−} mice have been utilized to investigate roles of CX3CL1 and CX3CR1 in various disease models (Ishida et al. 2008; Morimura et al. 2013; Yu et al. 2007). In the setting of wound healing, CX3CL1 is expressed by macrophages and endothelial cells, while CX3CR1 is expressed by macrophages and fibroblasts (Ishida et al. 2008). Decreased expression of macrophage-related cytokines such as TGF-β and vascular endothelial growth factor and reduced deposition of α-smooth muscle actin and collagen were shown in the wounded skin of CX3CR1^{−/−} mice (Ishida et al. 2008). The roles of CX3CL1 in tumor immunity was also studied using CX3CR1^{−/−} mice. CX3CR1^{−/−} mice injected with B16 melanoma cells had increased lung tumor burden together with selective reduction of monocytes and NK cells in the lungs (Yu et al.

Fig. 3 CX3CL1 expression on blood endothelial cells and infiltration of CX3CR1-expressing mast cells and neutrophils in the settings of vasculitis. CX3CL1-CX3CR1 interaction is also important for migration of resident macrophages

2007). Moreover, using mouse vasculitis model, we showed that the development of leukocytoclastic vasculitis was significantly reduced in $CX3CR1^{-/-}$ mice compared with WT mice (Morimura et al. 2013). Infiltration of neutrophils and mast cells as well as expression of IL-6 and TNF- α were decreased in $CX3CR1^{-/-}$ mice. Thus, knockout mouse models showed critical roles of CX3CL1 and CX3CR1 in wound healing, tumor immunity, and vasculitis.

The importance of interaction between CX3CL1 and CX3CR1 has been postulated in many inflammatory diseases, including rheumatoid arthritis, vasculitis, systemic sclerosis, and AD (Echigo et al. 2004; Hasegawa et al. 2005; Morimura et al. 2013; Murphy et al. 2008). Serum CX3CL1 levels and the frequencies of CX3CR1⁺ T cells in peripheral blood were significantly higher in patients with rheumatoid arthritis than in healthy controls (Murphy et al. 2008). Moreover, CX3CL1 levels in synovial fluid were elevated in rheumatoid arthritis, compared to osteoarthritis or healthy subjects. Serum CX3CL1 levels were also significantly higher in patients with vasculitis including polyarteritis nodosa than in healthy controls (Morimura et al. 2013). Upregulated expression of CX3CL1 and CX3CR1 in the affected tissue of systemic sclerosis may cooperatively augment the recruitment of mononuclear cells, leading to inflammation and vascular injury (Hasegawa et al. 2005). CX3CR1⁺ cells in the affected skin of patients with AD increased compared with those in normal skin and serum CX3CL1 levels were increased in AD patients, which were associated with the disease severity (Echigo et al. 2004). Thus, interaction between CX3CL1 and CX3CR1 plays important roles in the development of

rheumatoid arthritis, vasculitis, and AD. CX3CL1 expressed on blood endothelial cells can be a therapeutic target to prevent infiltration of CX3CR1⁺ immune cells such as mast cells, neutrophils, and macrophages (Fig. 3).

Conclusion

Many chemokines are involved in the development of skin diseases. They play important roles in establishing micro-environment in which migratory immune cells, together with skin-resident cells, cause prolonged inflammation. Some chemokines can also serve as an autocrine as well as a paracrine in skin malignancy. Biologics targeting chemokines and their receptors are promising strategies for various skin diseases that are resistant to the current therapy. Indeed, in Japan, anti-CCR4 monoclonal antibody is already approved in the treatment of recurrent ATLL and MF/SS. Although we cannot overlook potential side effects and relatively high prices, we should keep working hard to develop new drugs targeting chemokines or chemokine receptors to improve patients' life expectancy and quality of life.

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References

- Auffray C, Fogg DK, Narni-Mancinelli E et al (2009) CX3CR1⁺ CD115⁺ CD135⁺ common macrophage/DC precursors and the

- role of CX3CR1 in their response to inflammation. *J Exp Med* 206:595–606
- Baraniuk JN (1997) Pathogenesis of allergic rhinitis. *J Allergy Clin Immunol* 99:S763–772
- Bartels J, Schlüter C, Richter E et al (1996) Human dermal fibroblasts express eotaxin: molecular cloning, mRNA expression, and identification of eotaxin sequence variants. *Biochem Biophys Res Commun* 225:1045–1051
- Bazan JF, Bacon KB, Hardiman G et al (1997) A new class of membrane-bound chemokine with a CX3C motif. *Nature* 385:640–644
- Beaulieu S, Robbiani DF, Du X et al (2002) Expression of a functional eotaxin (CC chemokine ligand 11) receptor CCR3 by human dendritic cells. *J Immunol* 169:2925–2936
- Berkman N, Ohnana S, Chung FK et al (2001) Eotaxin-3 but not eotaxin gene expression is upregulated in asthmatics 24 hours after allergen challenge. *Am J Respir Cell Mol Biol* 24:682–687
- Campbell EM, Kunkel SL, Strieter RM et al (1998) Temporal role of chemokines in a murine model of cockroach allergen-induced airway hyperreactivity and eosinophilia. *J Immunol* 161:7047–7053
- Campbell JJ, Haraldsen G, Pan J et al (1999) The chemokine receptor CCR4 in vascular recognition by cutaneous but not intestinal memory T cells. *Nature* 400:776–780
- Charo IF, Ransohoff RM (2006) The many roles of chemokines and chemokine receptors in inflammation. *N Engl J Med* 354:610–621
- Chvatchko Y, Hoogewerf AJ, Meyer A et al (2000) A key role for CC chemokine receptor 4 in lipopolysaccharide-induced endotoxic shock. *J Exp Med* 191:1755–1764
- Echigo T, Hasegawa M, Shimada Y et al (2004) Expression of fractalkine and its receptor, CX3CR1, in atopic dermatitis: possible contribution to skin inflammation. *J Allergy Clin Immunol* 113:940–948
- Ferenczi K, Fuhlbrigge RC, Pinkus J et al (2002) Increased CCR4 expression in cutaneous T cell lymphoma. *J Invest Dermatol* 119:1405–1410
- Forssmann U, Uguccioni M, Loetscher P et al (1997) Eotaxin-2, a novel CC chemokine that is selective for the chemokine receptor CCR3, and acts like eotaxin on human eosinophil and basophil leukocytes. *J Exp Med* 185:2171–2176
- Fujimura T, Kambayashi Y, Furudate S et al (2014) A possible mechanism in the recruitment of eosinophils and Th2 cells through CD163(+) M2 macrophages in the lesional skin of eosinophilic cellulitis. *Eur J Dermatol* 24:180–185
- Fujita H, Asahina A, Sugaya M et al (2005) Differential production of Th1- and Th2-type chemokines by mouse Langerhans cells and splenic dendritic cells. *J Invest Dermatol* 124:343–350
- Ganzalo JA, Jia GQ, Aguirre V et al (1996) Mouse eotaxin expression parallels eosinophil accumulation during lung allergic inflammation but it is not restricted to a Th2-type response. *Immunity* 4:1–14
- Geissmann F, Jung S, Littman DR (2003) Blood monocytes consist of two principal subsets with distinct migratory properties. *Immunity* 19:71–82
- Godiska R, Chantry D, Raport CJ et al (1997) Human macrophage-derived chemokine (MDC) a novel chemoattractant for monocytes, monocyte-derived dendritic cells, and natural killer cells. *J Exp Med* 185:1595–1604
- Hasegawa M, Sato S, Echigo T et al (2005) Up regulated expression of fractalkine/CX3CL1 and CX3CR1 in patients with systemic sclerosis. *Ann Rheum Dis* 64:21–28
- Hoeck J, Woisetschlager M (2001) Activation of eotaxin-3/CCL26 gene expression in human dermal fibroblasts is mediated by STAT6. *J Immunol* 167:3216–3222
- Huax F, Gharaee-Kermani M, Liu T et al (2005) Role of Eotaxin-1 (CCL11) and CC chemokine receptor 3 (CCR3) in bleomycin-induced lung injury and fibrosis. *Am J Pathol* 167:1485–1496
- Imai T, Yoshida T, Baba M et al (1996) Molecular cloning of a novel T cell-directed CC chemokine expressed in thymus by signal sequence trap using Epstein–Barr virus vector. *J Biol Chem* 271:21514–21521
- Imai T, Hieshima K, Haskell C (1997) Identification and molecular characterization of fractalkine receptor CX3CR1, which mediates both leukocyte migration and adhesion. *Cell* 91:521–530
- Inngjerd M, Damaj B, Maghazachi AA (2000) Human NK cells express CC chemokine receptors 4 and 8 and respond to thymus and activation-regulated chemokine, macrophage-derived chemokine, and I-309. *J Immunol* 164:4048–4054
- Ishida Y, Gao JL, Murphy PM (2008) Chemokine receptor CX3CR1 mediates skin wound healing by prompting macrophage and fibroblast accumulation and function. *J Immunol* 180:569–579
- Ishida T, Joh T, Uike N et al (2012) Defucosylated anti-CCR4 monoclonal antibody (KW-0761) for relapsed adult T-cell leukemia-lymphoma: a multicenter phase II study. *J Clin Oncol* 30:837–842
- Ishii T, Ishida T, Utsunomiya A et al (2010) Defucosylated humanized anti-CCR4 monoclonal antibody KW-0761 as a novel immunotherapeutic agent for adult T-cell leukemia/lymphoma. *Clin Cancer Res* 16:1520–1531
- Johnson LA, Jackson DG (2013) The chemokine CX3CL1 promotes trafficking of dendritic cells through inflamed lymphatics. *J Cell Sci* 126:5259–5270
- Jung S, Aliberti J, Graemmel P et al (2000) Analysis of fractalkine receptor CX(3)CR1 function by targeted deletion and green fluorescent protein reporter gene insertion. *Mol Cell Biol* 20:4106–4114
- Kaburagi Y, Shimada Y, Nagaoka T et al (2001) Enhanced production of CC-chemokines (RANTES, MCP-1, MIP-1alpha, MIP-1beta, and eotaxin) in patients with atopic dermatitis. *Arch Dermatol Res* 293:350–355
- Kagami S, Kakinuma T, Saeki H et al (2003) Significant elevation of serum levels of eotaxin-3, but not of eotaxin-2/CCL24, in patients with atopic dermatitis: serum eotaxin-3 levels reflect the disease activity of atopic dermatitis. *Clin Exp Immunol* 134:309–313
- Kagami S, Kai H, Kakinuma T et al (2012) High levels of CCL26 in blister fluid and sera of patients with bullous pemphigoid. *J Invest Dermatol* 132:249–251
- Kakinuma T, Nakamura K, Wakugawa M et al (2001) Thymus and activation-regulated chemokine in atopic dermatitis: serum thymus and activation-regulated chemokine level is closely related with disease activity. *J Allergy Clin Immunol* 107:535–541
- Kakinuma T, Sugaya M, Nakamura K et al (2003) Thymus and activation-regulated chemokine (TARC/CCL17) in mycosis fungoides: serum TARC levels reflect the disease activity of mycosis fungoides. *J Am Acad Dermatol* 48:23–30
- Kawashima T, Tada Y, Asano Y et al (2010) Serum TARC/CCL17 levels are increased in dermatomyositis associated with interstitial lung disease. *J Dermatol Sci* 60:52–54
- Kimura T, Sugaya M, Suga H et al (2014) Variations in TARC and I-TAC are sensitive markers reflecting pruritus in atopic dermatitis. *Acta Derm Venereol* 94:331–332
- Kleinhans M, Tun-Kyi A, Gilliet M et al (2003) Functional expression of the eotaxin receptor CCR3 in CD30+ cutaneous T-cell lymphoma. *Blood* 101:1487–1493
- Lehtimäki S, Tillander S, Puustinen A et al (2010) Absence of CCR4 exacerbates skin inflammation in an oxazolone-induced contact hypersensitivity model. *J Invest Dermatol* 130:2743–2751

- Ma W, Bryce PJ, Humbles AA et al (2002) CCR3 is essential for skin eosinophilia and airway hyperresponsiveness in a murine model of allergic skin inflammation. *J Clin Invest* 109:621–628
- Miyagaki T, Sugaya M, Fujita H et al (2010) Eotaxins and CCR3 interaction regulates the Th2 environment of cutaneous T-cell lymphoma. *J Invest Dermatol* 130:2304–2311
- Miyagaki T, Sugaya M, Murakami T et al (2011) CCL11–CCR3 interactions promote survival of anaplastic large cell lymphoma cells via ERK1/2 activation. *Cancer Res* 71:2056–2065
- Morimura S, Sugaya M, Sato S (2013) Interaction between CX3CL1 and CX3CR1 regulates vasculitis induced by immune complex deposition. *Am J Pathol* 182:1640–1647
- Murphy G, Caplice N, Molloy M (2008) Fractalkine in rheumatoid arthritis: a review to date. *Rheumatology* 47:1446–1451
- Nakahigashi K, Doi H, Otsuka A et al (2012) PGD2 induces eotaxin-3 via PPAR γ from sebocytes: a possible pathogenesis of eosinophilic pustular folliculitis. *J Allergy Clin Immunol* 129:536–543
- Nakayama T, Watanabe Y, Oiso N et al (2010) Eotaxin-3/CC chemokine ligand 26 is a functional ligand for CX3CR1. *J Immunol* 185:6472–6479
- Ness TL, Ewing JL, Hogaboam CM et al (2006) CCR4 is a key modulator of innate immune responses. *J Immunol* 177:7531–7539
- Nickel R, Beck LA, Stellato C et al (1999) Chemokines and allergic diseases. *J Allergy Clin Immunol* 104:723–742
- Nishi N, Yamamoto S, Ou W et al (2008) Enhanced eotaxin-3 production by IL-4 through IFN- γ -induced upregulation of type 1 IL-4 receptor in keratinocytes. *Biochem Biophys Res Commun* 376:234–240
- Pope SM, Zimmermann N, Stringer KF et al (2005) The eotaxin chemokines and CCR3 are fundamental regulators of allergen-induced pulmonary eosinophilia. *J Immunol* 175:5341–5350
- Rothenberg ME, Luster AD, Leder P (1995) Murine eotaxin: an eosinophil chemoattractant inducible in endothelial cells and in interleukin 4-induced tumor suppression. *Proc Natl Acad Sci USA* 92:8960–8964
- Saeki H, Tamaki K (2006) Thymus and activation regulated chemokine (TARC)/CCL17 and skin diseases. *J Dermatol Sci* 43:75–84
- Sallusto F, Mackay CR, Lanzavecchia A (1997) Selective expression of the eotaxin receptor CCR3 by human T helper 2 cells. *Science* 277:2005–2007
- Sallusto F, Lenig D, Mackay CR et al (1998a) Flexible programs of chemokine receptors expression on human polarized T helper 1 and 2 lymphocytes. *J Exp Med* 187:875–883
- Sallusto F, Schaeferli P, Loetscher P et al (1998b) Rapid and coordinated switch in chemokine receptor expression during dendritic cell maturation. *Eur J Immunol* 28:2760–2769
- Shinkai A, Yoshisue H, Koike M et al (1999) A novel human CC chemokine, eotaxin-3, which is expressed in IL-4-stimulated vascular endothelial cells, exhibits potent activity toward eosinophils. *J Immunol* 163:1602–1610
- Sokolowska-Wojdylo M, Wenzel J et al (2005) Circulating clonal CLA(+) and CD4(+) T cells in Sézary syndrome express the skin-homing chemokine receptors CCR4 and CCR10 as well as the lymph node-homing chemokine receptor CCR7. *Br J Dermatol* 152:258–264
- Sugaya M (2010) Chemokines and cutaneous lymphoma. *J Dermatol Sci* 59:81–85
- Sugaya M, Nakamura K, Mitsui H et al (2003) Human keratinocytes express fractalkine/CX3CL1. *J Dermatol Sci* 31:179–187
- Tamaki K, Kakinuma T, Saeki H et al (2006) Serum levels of CCL17/TARC in various skin diseases. *J Dermatol* 33:300–302
- Trujillo G, O'Connor EC, Kunkel SL et al (2008) A novel mechanism for CCR4 in the regulation of macrophage activation in bleomycin-induced pulmonary fibrosis. *Am J Pathol* 172:1209–1221
- Tsunemi Y, Saeki H, Nakamura K et al (2006) CCL17 transgenic mice show an enhanced Th2-type response to both allergic and non-allergic stimuli. *Eur J Immunol* 36:2116–2127
- Uguccioni M, Mackay CR, Ochensberger B et al (1997) High expression of the chemokine receptor CCR3 in human blood basophils. Role in activation by eotaxin, MCP-4, and other chemokines. *J Clin Invest* 100:1137–1143
- Wakugawa M, Nakamura K, Kakinuma T et al (2001) CC chemokine receptor 4 expression on peripheral blood CD4+ T cells reflect disease activity of atopic dermatitis. *J Invest Dermatol* 117:188–196
- White GE, Greaves DR (2012) Fractalkine: a survivor's guide: chemokines as antiapoptotic mediators. *Arterioscler Thromb Vasc Biol* 32:589–594
- Xiao T, Fujita H, Saeki H et al (2003) Thymus and activation-regulated chemokine (TARC/CCL17) produced by mouse epidermal Langerhans cells is upregulated by TNF- α and IL-4 and downregulated by IFN- γ . *Cytokine* 23:126–132
- Yagi H, Seo N, Ohshima A et al (2006) Chemokine receptor expression in cutaneous T cell and NK/T-cell lymphomas: immunohistochemical staining and in vitro chemotactic assay. *Am J Surg Pathol* 30:1111–1119
- Yamaguchi T, Ohshima K, Karube K et al (2006) Expression of chemokines and chemokine receptors in cutaneous CD30+ lymphoproliferative disorders. *Br J Dermatol* 154:904–909
- Yang XP, Mattagajasingh S, Su S et al (2007) Fractalkine upregulates intercellular adhesion molecule-1 in endothelial cells through CX3CR1 and the Jak Stat5 pathway. *Circ Res* 101:1001–1008
- Yawalkar N, Uguccioni M, Schärer J et al (1999) Enhanced expression of eotaxin and CCR3 in atopic dermatitis. *J Invest Dermatol* 113:43–48
- Yokobayashi H, Sugaya M, Miyagaki T et al (2008) Serum chemokine levels in a case of angio-oedema associated with eosinophilia. *Br J Dermatol* 159:738–740
- Yokobayashi H, Sugaya M, Miyagaki T (2013) Analysis of serum chemokine levels in patients with HIV-associated eosinophilic folliculitis. *J Eur Acad Dermatol Venereol* 27:e212–216
- Yoshie O, Fujisawa R, Nakayama T et al (2002) Frequent expression of CCR4 in adult T-cell leukemia and human T-cell leukemia virus type 1-transformed T cells. *Blood* 99:1505–1511
- Yu B, Koga T, Urabe K et al (2002) Differential regulation of thymus and activation-regulated chemokine induced by IL-4, IL-13, TNF- α and IFN- γ in human keratinocyte and fibroblast. *J Dermatol Sci* 30:29–36
- Yu YR, Fong AM, Combadiere C et al (2007) Defective antitumor responses in CX3CR1-deficient mice. *Int J Cancer* 121:316–322