Expression and Function of CCL17 in Atopic Dermatitis

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1. Introduction

Chemokines are a superfamily of potent leukocyte chemoattractant cytokines with a molecular weight of 8-12 kDa. Historically, many chemokines had more than one name until the 1999 Keystone Symposium on Chemokines, when a new nomenclature was introduced (Zlotnik & Yoshie, 2000). Chemokines have been subdivided into four subfamilies on the basis of the position of either one or two cysteine residues located near the N-terminus of the protein and an L (ligand) was added (CXCL, CCL, CL and CXXXCL) to designate all chemokines as ligands of their respective receptors (R). The chemokine network comprises about 50 chemokines, as well as 20 classical (10 CCRs, 7 CXCRs, two XCR and a single CX3CR) and 3 atypical chemokine receptors (Duffy antigen receptor for chemokines = DARC, CC-X-chemokine receptor (CCX-CKR), and the D6 molecule) (Cyster, 2005; Comerford & McColl, 2011; Hansell & Nibbs, 2007; Ransohoff, 2009; Sallusto & Baggiolini, 2008). Many ligands bind multiple receptors, although each of them bind in a slightly different way, thereby inducing distinct downstream responses. The timing and venue of specific ligand-receptor interactions determines the nature of various biological processes. Although their best known function is the regulation of leukocyte migration, chemokines also enhance cell adhesion or costimulation, and stimulate myelopoiesis, tumor growth or angiogenesis (Ransohoff, 2009; Sallusto & Baggiolini, 2008; Viola & Luster, 2008). In addition, chemokines participate in the organization of the microenvironmental architecture of primary and secondary lymphoid organs during physiological and pathological conditions (Cyster, 2005). Importantly, a defined subset of chemokines and their receptors drive certain inflammatory immune responses to protect the body against microbial and environmental pathogens. Dysregulation of such chemokines may contribute to the pathogenesis of inflammatory diseases, like acute respiratory distress syndrome, multiple sclerosis, inflammatory bowel diseases, atherosclerosis, or rheumatoid arthritis (Charo & Ransohoff, 2006). Furthermore, chemokines produced in barrier organs are known to

substantially contribute to the pathogenesis of atopic diseases, like asthma, rhinitis and atopic dermatitis (D'Ambrosio, 2005; Homey et al., 2006; Pease, 2011).

1.1 Chemokine signaling

Chemokine receptors are pertussis toxin-sensitive heterotrimeric ($\alpha\beta\gamma$) G-protein coupled receptors (GPCR) with seven helical membrane-spanning regions connected by extra-membranous loops. Ligand binding induces a series of intracellular signalling pathways, leading to changes in actin cytoskeleton, activation of integrins, cell migration and alterations of the cellular activation status. For detailed information on chemokine receptor signaling pathways we refer the reader to other review articles covering this topic specifically (Randolph et al., 2008; Thelen & Stein, 2008; Wu, 2005). Briefly, chemokine ligand binding induces activation of the G proteins associated with the chemokine receptor causing the dissociation of G α -GTP from the receptor and from the G $\beta\gamma$ heterodimer. Whereas the G α subunit inhibits adenylyl cyclases, the G $\beta\gamma$ subunit is able to activate several effectors, including phosphatidylinositol-3-OH-kinase (PI3K) and members of the phospholipase C family. In addition, chemokine receptor signaling leads to activation of small GTPases of the Rho and Ras families.

1.2 Regulation of chemokine receptor expression

Many chemokine receptor genes are constitutively expressed and their cell surface expression ranges from as few as around 1000/cell in the case of CXCR4 to around 40,000/cell in the case of CXCR2 on neutrophils (Holmes et al., 1991; Loetscher et al., 1994). Chemokine receptor expression can be regulated by two major mechanisms: enhanced/reduced gene expression and/or desensitization. Altered gene expression of chemokine receptors is evident in naïve T lymphocytes expressing high levels of homeostatic receptors that mediate circulation through secondary lymphoid organs. Once activated, homeostatic receptors are down-regulated, and inflammatory chemokine receptors are up-regulated on effector cells (Ebert & McColl, 2002; Sallusto et al., 1998a). This allows effector cells to migrate into tissues where the ligands for the inflammatory receptors are being expressed. This mechanism also regulates DC trafficking into tissues, within tissues and from tissues into draining LN. Chemokine receptors may also undergo transient homologous or heterologous desensitization (Aragay et al., 1998; Mashikian et al., 1999). Binding of the ligand leads to phosphorylation-dependent internalization of the receptor and abolishes further chemokine stimulation. This is called homologous desensitization. In contrast, heterologous desensitization happens when molecules other than those that bind directly can desensitize chemokine receptors, for example by utilization of common intracellular signalling pathways, or by alterations in the phosphorylation status of the receptor.

2. Chemokine and chemokine receptor expression in AD

AD represents a chronic relapsing skin disease induced by epidermal barrier dysfunctions, sensitization to environmental allergens, microbial stimulation, and genetic predisposition (Bieber, 2008). The lesional skin contains many signs of leukocytic inflammation, resulting from enhanced production of proinflammatory cytokines and chemokines (Gros et al., 2009; Homey et al., 2006; Pastore et al., 2004). One of the initial events in the pathogenesis of AD is

a disturbance of the epidermal barrier and subsequent activation of keratinocytes by penetrating microbial and environmental pathogens or allergens. Release of pro-inflammatory cytokines, such as thymic stromal lymphopoietin (TSLP), IL-25 and IL-33 initially leads to the activation and/or attraction of innate immune cells, including cutaneous DC, and induction of a Th2-biased immune response (Carmi-Levy et al., 2011). During this phase a panel of homeostatic and inflammatory chemokines are upregulated in the affected skin areas, promoting the attraction of pro-allergic effector cells, like mast cells, eosinophils, inflammatory DC and cutaneous lymphocyte antigen (CLA)⁺CCR4⁺ skin-homing Th cells. Chemokines associated with an AD phenotype comprise CCL1, CCL2, CCL3, CCL5, CCL11, CCL13, CCL17, CCL18, CCL20, CCL22, CCL26, CCL27 and CX3CL1, and serum levels of CCL11, CCL17, CCL22, CCL26, CCL27 and CX3CL1 correlate with disease activity (Homey et al., 2006).

CCL1, CCL11 and CCL26 have been shown to interact with CCR8 and CCR3 on endothelial cells in AD, thereby inducing angiogenesis and tissue remodelling (Owczarek et al., 2010; Salcedo et al., 2001; Yawalkar et al., 1999). CCL1-CCR8 interactions also lead to recruitment of T cells and LC-like DC to the inflamed skin (Gombert et al., 2005), and have been associated with emigration of LC to the draining LN (Qu et al., 2004).

CCL27 is already expressed under homeostatic conditions and is further induced under inflammatory conditions in epidermal keratinocytes. In addition, CCL27 binds to the extracellular matrix and is displayed on endothelial cells in inflamed skin (Homey et al., 2002). CCR10, the receptor of CCL27, is preferentially expressed by CLA⁺CD4⁺ or CD8⁺ memory T cells (Hudak et al., 2002). Neutralization of CCL27 significantly inhibited inflammatory skin responses in mouse models that mimic allergic contact dermatitis and AD (Homey et al., 2002; Hudak et al., 2002). In addition to CCR10, the skin-homing CLA⁺ memory T cells express CCR4 on their cell surface. As further discussed below, CCR4 and CCR10 ligands cooperate in the recruitment of memory T cells to sites of skin inflammation (Mirshahpanah et al., 2008; Reiss et al., 2001).

The human chemokine CCL18 is one of the most highly expressed chemokines produced by DC in lesional skin of AD patients but not in psoriasis (Fujita et al., 2011; Gros et al., 2009; Pivarcsi et al., 2004). Pivarcsi et al. showed that allergen exposure, as well as staphylococcal products induced its expression *in vitro* and *in vivo*. Although the receptor of CCL18 is still unknown, this chemokine has been shown to attract CLA⁺ memory T cells (Günther et al., 2005).

3. Function and expression of CCL17

3.1 Classification of CCL17 as an inflammatory chemokine

The β -chemokine CCL17 formerly known as Thymus- and Activation Regulated Chemokine (TARC), was first identified as a T cell chemoattractant by the group of O. Yoshie in human thymus, and phytohemagglutinin stimulated peripheral blood mononuclear cells (Imai et al., 1996). Later on, the murine homologue was identified in murine bone marrow derived DC (BMDC) (Lieberman & Förster, 1999) and anti-CD40 stimulated splenic B cells (Schaniel et al., 1999). CCL17 shares the highest homology (32% amino acid identity) with CCL22 (macrophage-derived chemokine (MDC) and both chemokines signal through CCR4. CCR4 is expressed on T helper (Th)-1 and Th2 cells (D'Ambrosio et al., 1998; Sallusto et al., 1998a) but also on Th17 cells (Acosta-Rodriguez et al., 2007; Annunziato et al., 2007), CD8⁺ T cells (Kondo & Takiguchi, 2009; Semmling et al., 2010), regulatory T cells (Treg) (Iellem et al.,

2001), natural killer T (NKT) cells (Kim et al., 2002), NK cells (Inngjerdigen et al., 2000), platelets (Clemetson et al., 2000), eosinophils and monocytes (Bochner et al., 1999). Despite the broad expression pattern of CCR4, CCL17 has been mainly associated with Th2 type immune reactions and is implicated in the pathogenesis of several Th2-mediated diseases like atopic dermatitis (Sallusto et al., 1998a; Imai et al., 1999; Saeki & Tamaki, 2006). Besides attraction of Th2 cells, however, CCL17 may also induce chemotaxis of memory T cells, Treg and Th1 cells (Iellem et al., 2001; Lieberam & Förster, 1999). In addition, other CCR4-expressing cell types like CD8⁺ T cells, NK cells, basophils, eosinophils and DC may also respond to CCL17. As an inflammatory chemokine CCL17 is strongly upregulated in immature DC after stimulation with TLR ligands (Alferink et al., 2003; Lieberam & Förster, 1999). In addition, it can be upregulated following stimulation with various pro-inflammatory cytokines, as detailed below.

3.1.1 Transcriptional regulation of CCL17 expression

Whereas most CC chemokine genes are clustered on human chromosome 17 (mouse chromosome 11), *ccl17* is located downstream of *ccl22* and *cx3cl1* on the human chromosome 16q13 and mouse chromosome 8q (Hiroshima et al., 2001). The promoter region of *ccl17* contains several transcriptional regulation sites, like signal transducer and activator of transcription (STAT)6 binding sites and a nuclear factor kappa B (NF- κ B) site (Liddiard et al., 2006; Liu et al., 2007; Monick et al., 2007; Nakayama et al., 2004; Wirnsberger et al., 2006). Expression of CCL17 is induced by the Th2 cytokines interleukin (IL)-4 and IL-13 via STAT6, and NF- κ B activation occurs in response to TLR signaling. In the case of CCL17 expression, both pathways appear to act synergistically (Monick et al., 2007). In addition, other cytokines, like tumor necrosis factor (TNF)- α , granulocyte/macrophage colony stimulating factor (GM-CSF), and TSLP have also been shown to upregulate CCL17 expression (Heijink et al., 2007; Imai et al., 1999; Liu et al., 2007; Soumelis et al., 2002; Wirnsberger et al., 2006; Xiao et al., 2003). TSLP is an IL-7-like cytokine produced mainly by keratinocytes in an inflammatory environment. TSLP induces maturation of myeloid DC, which in turn produce CCL17 and CCL22. In contrast, Interferon gamma (IFN- γ) has been shown to act as a counter regulator of CCL17 production (Fujita et al., 2005; Xiao et al., 2003), although this cytokine enhances CCL17 expression in conjunction with TNF- α in the HaCaT keratinocyte cell line (Vestergaard et al., 2001). A unique feature of murine CCL17 is that additionally to its own promoter, transcription in brain and kidney may be initiated from the promoter of the closely linked CX3CL1 (fractalkine) gene, resulting in expression of a protein containing the CX3CL1 signal sequence and the CCL17 coding region (Hiroshima et al., 2001).

3.2 Cell-type specificity of CCL17 expression in human and mouse

In mice, mature CD11c⁺CD8-CD11b⁺ myeloid DC represent the predominant source of CCL17 production. Under steady state conditions, CCL17 is highly expressed in DC of the thymus, peripheral and mesenteric LN, small intestine, colon, and lung (Alferink et al., 2003). Apart from the thymus, all of these organs are associated with environmental barriers. The expression pattern of CCL17 emphasizes its importance in mediating the attraction of immune cells to sites, which are frequently exposed to environmental pathogens or allergens. Interestingly, CCL17 expression is normally not found in the spleen, even after systemic LPS challenge (Alferink et al., 2003). The only agent identified so far,

which is able to strongly induce CCL17 in splenic DC, is the synthetic glycolipid α -galactosylceramide, a well known CD1d-dependent inducer of NKT cell activation (Semmling et al., 2010). After licensing by activated NKT cells, cross-priming CD8⁺ DC produce CCL17 and attract naïve cytotoxic T cells expressing CCR4. Based on the analysis of CCL17/EGFP reporter mice, expression of CCL17 is fairly restricted to DC and has not been observed in keratinocytes, B cells, endothelial or epithelial cells. Dermal DC (dDC) and LC in normal, untreated skin of mice are also CCL17-negative but turn on CCL17 expression following irritation or injury of the skin (Stutte et al., 2010).

Although healthy human skin is devoid of CCL17 expression as well, human keratinocytes were shown to express CCL17 in inflamed skin, such as lesional skin of AD patients (Kakinuma et al., 2001; Vestergaard et al., 2000). *In vitro*, CCL17 expression is also found constitutively in HaCaT cells and is further inducible by cytokine stimulation (Vestergaard et al., 2001), whereas normal human keratinocytes did not express CCL17 protein *in vitro*, even after cytokine stimulation (Tsuda et al., 2003; Saeki & Tamaki, 2006). In contrast, human LC, Inflammatory Dendritic Epidermal Cells (IDEC) and dDC strongly express CCL17 (and CCL22) in inflammatory environments, particularly in lesional skin of AD patients, as do LPS stimulated human monocyte-derived DC (D'Ambrosio et al., 2002; Fujita et al., 2011; Kang et al., 2010; Soumelis et al., 2002). In addition, non-haematopoietic cells, such as bronchial epithelial cells, endothelial cells, fibroblasts, as well as smooth muscle cells can be a source of inducible CCL17 in humans (D'Ambrosio et al., 2002; Faffe et al., 2003; Sekiya et al., 2003; Yu et al., 2002). Taken together, under inflammatory conditions CCL17 appears much more widely expressed in different cell-types in human as opposed to mice, where CCL17 expression is quite restricted to DC subsets. However, detection of CCL17 protein expression by immunohistology as it has frequently been performed in human studies, may also pick up CCL17 that is passively absorbed to the cell membrane, for example by adhesion to surface glycosaminoglycans, and may not necessarily reflect transcription of the *ccl17* gene in the same cell-type.

3.3 Clearance of CCL17

CCL17 interacts with two chemokine decoy receptors, the Duffy antigen (DARC) and the D6 receptor. The Duffy antigen is found on red blood cells and binds both CC and CXC chemokines. In contrast, D6 is expressed on lymphatic endothelial cells in skin, gut and lung and interacts with inflammatory CC chemokines only. Although D6 is structurally similar to other chemokine receptors, it is most homologous to CCR4 and CCR5. Ligand binding induces rapid internalization of the ligand-receptor complexes, which facilitates regulation of inflammatory immune responses and enables the final return to homeostatic levels. Interestingly, the homeostatic chemokines CCL19 and CCL21 cannot efficiently bind D6 (Bonecchi et al., 2004). Instead, CCL19, CCL21 and CCL25 are able to bind with high affinity to another hepta-helical surface protein, termed CCX-CKR, which also acts as a chemokine scavenger (Comerford et al., 2006; Gosling et al., 2000).

4. CCL17 in atopic dermatitis

AD is one of the most frequent chronic inflammatory skin diseases in children and adults and is characterized by pruritic skin lesions in typical body areas such as the flexural folds on dry skin (Bieber, 2008). Various exogenous and endogenous factors, including allergens

and microbial antigens have been identified as triggers of acute flare ups of the disease as well as risk factors for severe persistent courses (Novak & Simon, 2011). In addition, a multitude of genetic modifications impact on disease manifestation, including a partially genetically predetermined disturbed skin barrier (Barnes, 2010; O'Regan & Irvine, 2010). Not only lesional AD skin, but also clinically non-lesional skin of AD patients displays multiple histologic as well as immunologic differences as compared to the skin of healthy individuals (Suárez-Fariñas et al., 2011). One of those differences is the expression of the high affinity receptor for IgE (FcεRI) on the surface of skin DC. While FcεRI⁺ LC are present in non-lesional AD skin, development of skin lesions goes along with the infiltration of the epidermis by another CD1a⁺ myeloid DC subpopulation, highly expressing FcεRI but negative for Birbeck granules and respective Langerin expression, which have been characterized as IDEC (Novak & Bieber, 2005; Wollenberg et al., 1995).

As mentioned above, a large number of chemokines have been found to be upregulated in lesional skin and serum of AD patients and several chemokine-chemokine receptor pairs have been linked to the pathogenesis of AD, in particular CCL1-CCR8, CCL17/CCL22-CCR4, CCL18, CCL20-CCR6, and CCL27-CCR10 (Gros et al., 2009; Homey et al., 2006; Pastore et al., 2004; Pease & Williams, 2006). In AD, chemokines regulate the emigration of DC to the draining LN as well as the attraction of activated T cells, eosinophils, basophils and mast cells to the site of inflammation. In the following, we will focus on the role of the two CCR4 ligands CCL17 (TARC) and CCL22 (MDC) as biomarkers of disease severity in AD, and the functional influence of these chemokines on the pathogenesis of AD.

4.1 CCL17 as a biomarker for disease severity in AD

The first indication that CCL17 is upregulated in lesional AD skin came from the analysis of inflamed skin from NC/Nga mice, which spontaneously develop AD-like skin lesions (Vestergaard et al., 1999). Soon after that, enhanced frequencies of CLA⁺CCR4⁺ T lymphocytes were detected in the blood of AD patients, as well as a localized upregulation of CCL17 in the basal layers of the epidermis in lesional skin, presumably in keratinocytes (Vestergaard et al., 2000). Later on, numerous clinical studies demonstrated that CCL17 levels in serum of AD patients and the presence of CCL17 in lesional skin correlate with disease activity (for review see (Saeki & Tamaki, 2006)). As shown recently, expression of both, CCL17 as well as CCL22 is higher in LC and IDEC of patients with AD as compared to LC in healthy skin or epidermal DC isolated from the epidermis of patients with other chronic inflammatory skin diseases such as psoriasis (Fujita et al., 2011). Moreover, even dermal DC in AD express higher levels of CCL17 and CCL22. The selective upregulation of those chemokines in DC in AD skin further supports the concept of CCL17 and CCL22 being crucial for the recruitment of Th2 cells, which predominate in particular in the acute phase of the disease (Grewe et al., 1998). Sequential biopsies taken from the same individuals during atopy patch testing revealed more detailed insights into the kinetics and nature of chemokine upregulation in the skin during early and late phases of eczema development. For this diagnostic test, allergens are applied to the skin occlusively for 24 hours and eczema develops within 24-72 hours in the region of allergen application in sensitized individuals (Darsow et al., 1996). Expression of CCL17 and CCL22 is among other chemokines rapidly upregulated on the mRNA level already 24 hours later and increases further during the following 48 hours. In parallel, the number of inflammatory DC subtypes in the epidermis as well as T cells in the dermis increases

(Gros et al., 2009). The intensity of chemokine upregulation as well as the pattern of chemokines induced seem to be decisive for the development of eczematous skin lesions. Consequently, it is very likely that improvement of the skin lesions will occur in parallel with the reduction in amount of particular chemokines in the skin, leading to the discontinuation of the recruitment of inflammatory cell subtypes. In line with this, treatment of AD patients by immunotherapy (Bussmann et al., 2007; Kwon et al., 2010), or culture of PBMC with antihistamines (Furukawa et al., 2004; Shoji et al., 2011) leads to a significant reduction of CCL17 expression. Recently, immunofluorescence detection of CCL17 in the skin of AD patients showed that CCL17 expression levels in the stratum corneum correlate with disease activity as well (Morita et al., 2010). As for CCL17, similar findings have been obtained for the other CCR4 ligand CCL22 (Goebeler et al., 2001; Shimada et al., 2004), although CCL17 or CCL22 appear to be expressed by different cell types in the skin as determined by immunohistology (Vestergaard et al., 1999). Whereas CCL17 expression was mostly located to the basal layers of the epidermis, CCL22 expression was predominantly found in dermal cells. In addition, Hashimoto et al. described CCL22 to be more strongly upregulated in human monocyte-derived DC isolated from AD patients than CCL17, when compared to expression levels in healthy controls (Hashimoto et al., 2006).

Interestingly, the keratinocyte-derived cytokine TSLP, which is strongly upregulated in the epidermis of AD lesional skin specifically induces CCL17 and CCL22 expression in human peripheral blood CD11c⁺ DC (Soumelis et al., 2002) as well as human epidermal LC (Ebner et al., 2007). TSLP expression levels in the skin also correlated with enhanced migratory activity of LC (Guttman-Yassky et al., 2007; Soumelis et al., 2002). A possible link between skin barrier dysfunction and CCL17 was recently reported by Nakahigashi et al., who showed that CCL17 was able to induce aquaporin-3 in human keratinocytes, which in turn promoted keratinocyte proliferation and disturbed barrier function (Nakahigashi et al., 2010).

Whereas elevated levels of CCL17 and CCL22 have also been observed in allergic contact dermatitis (Bäumer et al., 2004; Goebeler et al., 2001; Kamsteeg et al., 2010; Martín et al., 2002), CCL17/CCL22 expression is not significantly increased in Psoriasis vulgaris (Gros et al., 2009; Kakinuma et al., 2002; Kamsteeg et al., 2010; Saeki & Tamaki, 2006; Uchida et al., 2002). This correlates with the fact that psoriasis is a Th1 dominated disease, whereas Th2-type cytokines and chemokines dominate the initial phase of AD, with a shift to Th1-type cytokines in the chronic phase (Grewe et al., 1998; Fujita et al., 2011). In psoriasis, Th17 cells act together with Th1 cells in disease pathogenesis (Lowes et al., 2008; Nograles et al., 2009). The Th17 T cell subset has also been detected at enhanced frequencies in lesional skin and peripheral blood of AD patients, mainly in the acute phase of the disease (Koga et al., 2008; Toda et al., 2003). In addition, IL-17 was found to be produced by T cells infiltrating the skin of filaggrin-deficient mice (Oyoshi et al., 2009). In another study, however, T22 cells, which produce IL-22 but not IL-17, rather than Th17 cells were reported to be especially increased in AD as opposed to psoriasis (Nograles et al., 2009). In line with this, Hayashida et al. reported that the presence of Th17 cells negatively correlated with CCL17 and IgE levels in AD patients, whereas serum IL-22 levels positively correlated with those of CCL17 (Hayashida et al., 2011a; 2011b). Whereas IL-17 has proinflammatory and anti-microbial effects, IL-22 inhibits terminal differentiation of keratinocytes and enhances epidermal hyperplasia (Nograles et al., 2008).

4.2 Pathogenic role of CCL17 in mouse models of AD

To study the mechanism of action of CCL17 in the pathogenesis of AD several mouse models have been employed. In general, mouse models of AD can be classified into spontaneous or intentional genetic mutants, and AD models induced by chronic treatment of wild-type or genetically modified mouse strains with epicutaneous allergens (for review see (Jin et al., 2009a)). There are two major spontaneous mouse models of AD, the NC/Nga (Matsuda et al., 1997) and the flaky tail mice (Fallon et al., 2009; Moniaga et al., 2010). In NC/Nga mice, dermatitis occurs only when the animals are kept under conventional breeding conditions but not under specified pathogen free conditions (Vestergaard et al., 1999), indicating that both genetic and environmental factors contribute to disease pathogenesis. In this mouse strain upregulation of CCL17 and CCL22 in lesional skin was first described (Vestergaard et al., 1999). Flaky tail mice harbor a single base pair nonsense mutation in the filaggrin gene, mimicking similar mutations found in AD patients (Fallon et al., 2009; Moniaga et al., 2010). Filaggrin deficiency results in an outside-to-inside skin barrier dysfunction and development of AD symptoms. In a modification of the original AD mouse model induced by chronic epicutaneous application of ovalbumin (OVA) as a model allergen (Spergel et al., 1998), a skin barrier dysfunction is induced by repeated tape-stripping of the skin, which disrupts the upper layers of the epidermis (Wang et al., 2007). Using our CCL17/EGFP reporter mice we could show that such mechanical irritation of the skin already leads to upregulation of CCL17 expression in cutaneous DC, as does epicutaneous treatment with DNFB, whereas CCL17 is not expressed in untreated skin (Alferink et al., 2003; Stutte et al., 2010). Upregulated expression of CCL17 in the skin was also observed in a transgenic mouse model of AD based on inducible expression of TSLP in keratinocytes. In this model only *ccl17* but not *ccl22* mRNA was increased in the skin (Yoo et al., 2005). To directly study the pathogenic effects of constitutive CCL17 expression in the skin, Tamaki and colleagues generated transgenic mice, in which *ccl17* is expressed under control of the human keratin 14 promoter. Expression of CCL17 in keratinocytes did not induce skin inflammation as such, whereas contact hypersensitivity (CHS) responses were differentially modulated by CCL17 depending on the contact sensitizer. In addition, increased numbers of Th2 cells and mast cells were recruited to the skin, and serum IgE levels were elevated (Tsunemi et al., 2006). Thus, when inflammation was induced by allergic sensitizers or irritants, CCL17 modified the inflammatory response and enhanced AD-like symptoms.

To obtain further insight into the pathogenic role of CCL17 in AD, we analyzed the development of AD-like symptoms in wild-type, CCL17/EGFP-reporter and CCL17-knockout mice after tape-stripping of the skin and chronic application of OVA (Stutte et al., 2010). In this model, a small area of the back skin was tape-stripped and a patch soaked with OVA was applied to the skin for three consecutive periods of one week, separated by two week breaks. Sham treated mice showed no signs of AD, whereas OVA treatment lead to acanthosis and thickening of the dermal layer. We found that CCL17-deficiency significantly diminished dermal infiltration with mast cells, eosinophils and CD4 T cells, whereas the development of acanthosis was unaffected. OVA-specific IgG and IgE antibody production was decreased and levels of inflammatory cytokines in the draining LN and in the skin were significantly reduced. Taken together, the majority of AD symptoms were strongly ameliorated in CCL17-deficient mice (Stutte et al., 2010). In addition, we made the unexpected and interesting observation that LC of CCL17-deficient mice failed to emigrate

from the affected skin area, despite the presence of acanthosis, which is indicative of an ongoing inflammatory process. This finding was also supported by the fact that OVA-treated CCL17-knockout mice had reduced total numbers of skin-derived DC in the draining LN. Furthermore, we tested the ability of LC to emigrate from the skin using epidermal sheets of DNFB sensitized ear skin. As already observed in the AD model, CCL17-deficient LC were strongly impaired in emigration from the epidermis in this short-term assay. In contrast, LC emigration could be restored when recombinant (r) CCL17 was injected into the ear skin prior to DNFB treatment (Stutte et al., 2010). Thus, we could show that CCL17 is instrumental for the emigration of LC from the skin to the draining LN. Based on the reduced numbers of skin-derived DC in draining LN of OVA-treated CCL17-deficient mice, it might be possible that the migration of dDC is also affected by CCL17. The main conclusion from these experiments is that CCL17 contributes to the pathogenesis of AD in two different ways: i) upregulation of the inflammatory chemokine CCL17 in cutaneous DC is essential for LC emigration from the skin and thus for priming of immune responses in the draining LN, and ii) CCL17 (together with other chemokines, such as CCL22 and CCL27) enhances the attraction of activated T cells from the circulation to the inflamed skin. Our finding on the role of CCL17 in the induction of LC emigration is in line with histological observations in the skin of AD patients that expression of TSLP, a major inducer of CCL17, correlates with enhanced migratory activity of LC (Guttman-Yassky et al., 2007; Soumelis et al., 2002). Already in 2001, Katou et al. reported that about 50% of LC in inflamed skin but not dermal DC express the CCR4 receptor, suggesting that CCR4 ligands also influence LC migration (Katou et al., 2001).

4.2.1 Molecular processes involved in emigration of DC from the skin

To access non-lymphoid peripheral tissues, immature DC utilize specific chemokine receptor-ligand interactions, such as CCR2-CCL2, CCR5-CCL5 and CCR6-CCL20. In the periphery they are mostly sessile and constantly scan for antigens. Once stimulated, peripheral DC mature and actively migrate to the draining LN, where they act as professional antigen-presenting cells to prime naïve T cells and initiate antigen-specific responses. LC are located in between the basal keratinocyte layers of the epidermis and sample antigens that penetrated through the outer skin barrier – the stratum corneum. In the presence of danger signals induced by recognition of chemical or microbial antigens, or by physical stress, the sequential process of LC emigration from the skin to the draining LN is initiated. This process can be divided into the phases of mobilization, detachment, penetration of the basal membrane, interstitial migration within the dermis, traversing of the afferent lymphatic endothelium and transit to the LN within the lymphatic vessel (for review see (Alvarez et al., 2008)). Mobilization of LC is initiated by the pro-inflammatory cytokines TNF- α and IL-1 β , and passage through the basal membrane depends on the presence of matrix metalloproteinases (MMP), like MMP-2 and MMP-9 (Ratzinger et al., 2002). Epicutaneous sensitization increases CXCR4 and CCR7 expression on cutaneous DC (Dieu et al., 1998; Sallusto et al., 1998b; Sozzani et al., 1998). Blocking experiments with CXCR4 antagonists showed that CXCL12-CXCR4 interactions are required for transit of LC from the epidermis to the dermis (Kabashima et al., 2007), whereas CCR7 appears not to be essential for this step but rather for entry of the cells into the afferent lymphatics from the dermis (Ohl et al., 2004). In addition, CCL1-CCR8 interactions may also be involved in the migration of DC from the skin to the LN (Qu et al., 2004).

Because of the impaired emigration of LC from the skin of CCL17-deficient mice in models of AD and CHS, we analyzed the responsiveness of CCL17-deficient BMDC to the CCR7 ligands CCL19 and CCL21, and the CXCR4 ligand CXCL12 in *in vitro* migration assays. In a transwell assay as well as a 3D migration assay in collagen gels, migration of CCL17-deficient BMDC was partially impaired as compared to heterozygous control cells (Stutte et al., 2010). This migratory deficiency could be fully restored by addition of rCCL17 or rCCL22 to the cultures in a time- and concentration dependent manner. Because we did not detect major differences in the level of CCR7 expression, we hypothesized that CCL17 sensitizes CCR7 and CXCR4 for optimal responsiveness to their ligands, as previously reported for prostaglandin E₂ (PGE₂) in the case of CCR7 (Sánchez-Sánchez et al., 2006; Scandella et al., 2004). In this context, it is interesting that histamine and PGE₂ were shown to upregulate CCL17 and CCL22 production in human myeloid DC (McIlroy et al., 2006). In addition to the observed changes in chemokine responsiveness of CCL17-deficient BMDC, a potential influence of CCL17 on the initial steps of LC emigration from the epidermis, like mobilization and detachment, as well as the production of MMP and penetration of the basal membrane still need to be investigated. Enzymatic activity of MMP-2 in epidermal and dermal cell suspensions was shown to be increased by IL-21 in wild-type but not IL-21 receptor (IL-21R)-deficient mice. Of note, AD-like symptoms, *ccl17* mRNA expression in OVA-treated skin, and migration of cutaneous DC to CCR7 ligands were also reduced in IL-21RKO mice (Jin et al., 2009b).

4.2.2 Phenotypic differences of CCL17- and CCR4-deficient mice

Because both CCL17 and CCL22 bind to CCR4 and thus may have redundant functions, one might anticipate that the amelioration of AD symptoms would be even more pronounced in CCR4-deficient mice compared to CCL17-deficient mice. Surprisingly, CCR4 knockout mice were not protected from the development of AD-like symptoms and exhibited normal emigration of DC from the skin after epicutaneous treatment with a contact sensitizer (Stutte et al., 2010). Similar findings were also reported by another group, showing that deficiency of CCR4 had no phenotype in the AD model, whereas absence of CCL8-CCR8 interactions diminished AD pathology (Islam et al., 2011). One possible explanation for this finding is the existence of an additional, as yet unknown receptor for CCL17. Inngjerdingen et al. demonstrated that CCL17 binding completely desensitized a calcium flux induced by CCL22, whereas CCL22 only partially reduced the calcium release to CCL17 (Inngjerdingen et al., 2000), indicating a different receptor binding activity of the two chemokines, or the presence of a second receptor for CCL17. In some studies, CCR8 was reported to function as a receptor for CCL17 (Bernardini et al., 1998; Inngjerdingen et al., 2000), but this finding is controversial and was disproven by others (Garlisi et al., 1999). For unknown reasons, genetic ablation of CCR4 also resulted in a deficiency of splenocytes to migrate to CCL3 (MIP-1 α) (Chvatchko et al., 2000), which may also affect the phenotype of CCR4 knockout mice.

Another explanation for the different phenotype of CCL17- and CCR4-knockout mice may lie in differential expression patterns (Hashimoto et al., 2006; Vestergaard et al., 1999; 2000) and partially opposing functions of CCL17 and CCL22. In particular, CCL22-CCR4 interactions have been associated with enhanced recruitment of Treg (Curiel et al., 2004), whereas CCL17 appears to restrict the expansion of Treg in a mouse model of atherosclerosis (Weber et al., 2011). Furthermore, CCL22 is more potent in inducing

integrin-dependent adhesion of CCR4⁺ Th cells (D'Ambrosio et al., 2002) and very rapidly induces CCR4 desensitization and receptor internalization from the cell surface. Thus, treatment of human Th2 cells with 1000 ng/ml CCL22 was sufficient to induce 90% internalization of CCR4, whereas no more than 20% CCR4 internalization was triggered by the same amount of CCL17 (Mariani et al., 2004). D'Ambrosio et al. also suggested that CCL17 and CCL22 may act sequentially in the course of T cell extravasation into the skin, because only CCL17 is presented by endothelial cells in skin vessel, whereas CCL22 is more dominantly expressed in interstitial DC (D'Ambrosio et al., 2002). Another difference between CCL17 and CCL22 was reported regarding their ability to bind to the decoy receptor D6. Full length CCL22 had a much higher affinity to D6 than CCL17, and cleavage of CCL22 by the dipeptidyl-peptidase IV completely prevented binding to D6 (Bonecchi et al., 2004).

Taken together, CCL17 and CCL22 appear to be non-redundant in many aspects and differential, cell-type specific expression of these two chemokines may additionally account for the fact that genetic deficiency of CCL17 cannot be compensated by CCL22 *in vivo* (Stutte et al., 2010). On the other hand, targeting of CCR4 may have opposing effects on the immune response, as CCR4 is involved in both the attraction of pro-inflammatory T cells and of immunosuppressive Treg.

5. Implication of CCL17, CCL22 and CCR4 in other diseases

In addition to AD, enhanced expression of CCL17 and CCL22, as well as elevated frequencies of CCR4⁺ T cells have been observed in asthma (Panina-Bordignon et al., 2001; Vijayanand et al., 2010) and rhinitis (Takeuchi et al., 2005; Terada et al., 2001), the two other forms of atopic diseases. In the case of asthma the pathogenic role of the CCL17/CCL22-CCR4 axis is still controversial (Pease, 2006), as some reports demonstrate efficient improvement of disease symptoms after CCR4 or CCL17 blockade (Kawasaki et al., 2001; Perros et al., 2009; Vijayanand et al., 2010), whereas others do not (Chvatchko et al., 2000; Conroy et al., 2003). As already mentioned above, enhanced expression of CCL17 and CCL22 has also been observed in allergic contact dermatitis (Bäumer et al., 2004; Goebeler et al., 2001; Kamsteeg et al., 2010; Martín et al., 2002), and contact hypersensitivity responses were significantly inhibited in CCL17-deficient mice (Alferink et al., 2003). Regarding non-allergic diseases, CCL17 has recently been shown to enhance the formation of atherosclerotic lesions in mice by inhibition of Treg cell expansion (Weber et al., 2011). Furthermore, deficiency in CCL17 or CCR4 prolongs graft survival in mouse models of cardiac allograft rejection (Alferink et al., 2003; Hüser et al., 2005).

As CCL17 expression is strongly upregulated in response to TLR stimulation (Lieberman & Förster, 1999; Alferink et al., 2003), it is possible that this chemokine is also involved in the defence against microbial infections. After cutaneous infection with the murine filaria *Litomosoides sigmodontis*, CCL17 was shown to control filarial worm load as a consequence of reduced mast cell dependent larval entry (Specht et al., 2011). In contrast, blockade of CCL17 but not CCL22 enhanced protection from murine pulmonary aspergillosis, and CCR4-deficient mice were similarly protected (Carpenter & Hogaboam, 2005). CCL17 production induced by NKT cell activation licensed splenic DC for efficient cross-presentation of OVA and stimulation of CTL responses (Semmling et al., 2010). Thus, CCL17 may also be involved in the defence against viral infections, although this has not been directly assessed so far.

6. Perspectives on chemokines and chemokine receptors as therapeutic targets in AD

Because of the crucial role of chemokine/chemokine-receptor interactions in the pathogenesis of allergic responses, it seems very attractive to use specific inhibitors, like neutralizing antibodies or small molecule antagonists, as therapeutic drugs to prevent or dampen the inflammatory reaction. Many inhibitors of chemokines and their receptors have already been developed and are currently tested in various disease models and in clinical studies (for recent reviews see (Garin & Proudfoot, 2011; Mackay, 2008; Pease, 2011)). However, the pleiotropic action of many chemokines and the frequent redundancies in the system hamper the development of efficient drugs and their approval for clinical use. Nevertheless, there is still optimism that chemokines and their receptors are promising targets for treatment of inflammatory diseases.

In the case of CCR4 at least four different small molecule inhibitors have been developed and successfully tested *in vitro* as well as in T cell migration models in mice (Nakagami et al., 2010; Pease, 2011; Sato et al., 2009). As indicated by the fact that CCR4 knockout mice develop AD-like symptoms (Islam et al., 2011; Stutte et al., 2010) and OVA-induced lung inflammation (Chvatchko et al., 2000) comparable to wild-type mice, blockade of CCR4 alone may not be sufficient to prevent these allergic reactions. In two studies addressing skin inflammation, simultaneous blockade of CCR4- and CCR10-ligands, or of CCR4 and the CCR10 ligand CCL27 was shown to be required for efficient inhibition of contact hypersensitivity at the time of challenge, or for homing of allergen-specific T cells to the skin (Mirshahpanah et al., 2008; Reiss et al., 2001). In another study, however, treatment with anti-CCL27 alone led to a significant inhibition of CHS and development of AD-like symptoms (Homey et al., 2002). As discussed above the amelioration of AD symptoms in CCL17-deficient mice but not CCR4-deficient mice indicates the presence of an additional receptor for CCL17, in particular with relevance for the emigration of LC from the skin. In addition, differences in the function of CCL17 and CCL22 regarding the attraction of Treg versus T helper cells may limit the usefulness of CCR4 antagonists in the treatment of allergic reactions. In fact, CCR4 blockade has also been proposed as a means to reduce attraction of tumor infiltrating Treg in cancer therapy (Yang et al., 2011). Therefore, it may be reasonable to also consider neutralization of certain chemokine ligands like CCL17 and CCL27 for therapy of AD, as an alternative to the blockade of chemokine receptors.

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8. References

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Atopic Dermatitis is a common disease characterized by inflamed, itching and dry skin. This relapsing allergic disorder has complex etiology and shows a remarkably high clinical heterogeneity which complicates the diagnosis and clinical management. This book is divided into 4 sections. The first section (Disease Etiology) describes some of the physiological mechanisms underlying Atopic Dermatitis, including alterations in the immune system and the skin-barrier function. The important role of host-microorganism interactions on the pathophysiology of Atopic Dermatitis is discussed in the second section (Microorganisms in Atopic Dermatitis). An overview of the clinical diagnostic criteria and the disease management protocols commonly used is given in the third section (Diagnosis and Clinical Management). The last section (New Treatments) describes new therapeutic approaches that are not widely used but are currently being studied due to preliminary evidence showing a clinical benefit for Atopic Dermatitis.

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