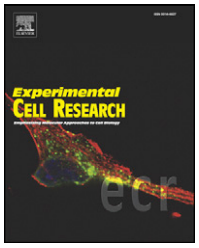
EXPERIMENTAL CELL RESEARCH 317 (2011) 613–619

available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/yexcr



Review

CCR6 as a mediator of immunity in the lung and gut☆

*Toshihiro Ito, William F. Carson IV, Karen A. Cavassani, Judith M. Connett, Steven L. Kunkel**

Department of Pathology, University of Michigan Medical School, Ann Arbor, MI 48109-2200, USA

ARTICLE INFORMATION

Article Chronology:
Received 4 October 2010
Revised version received
20 December 2010
Accepted 20 December 2010

Keywords:
CCR6
Innate immunity
Mucosal immunity
Dendritic cell

ABSTRACT

Chemokines are key mediators of leukocyte recruitment during pathogenic insult and also play a prominent role in homeostasis. While most chemokine receptors bind to multiple chemokines, CCR6 is unique in that this receptor is one of only a few that can bind only a single chemokine ligand, CCL20. CCR6 is an important receptor that is involved in regulating several aspects of mucosal immunity, including the ability to mediate the recruitment of immature dendritic cells (DCs) and mature DCs, and professional antigen presenting cells (APCs) to the sites of epithelial inflammation. Further, CCR6 mediates the homing of both $CD4^+$ T (T-helper; Th) cells and DCs to the gut mucosal lymphoid tissue. DCs, which are known to be essential immune cells in innate immunity and in the initiation of adaptive immunity, play a central role in initiating a primary immune response. Herein, we summarize the role of CCR6 in immune responses at epithelial and mucosal sites in both the lung and gut based on a review of the current literature.

© 2011 Elsevier Inc. All rights reserved.

Contents

Introduction

Chemokines constitute a family of structurally related chemotactic cytokines that direct the migration of leukocytes throughout the body under both physiological and inflammatory conditions [1,2]. Interestingly, while most chemokine receptors bind to multiple chemokines, the chemokine receptor CCR6 has only one chemokine ligand, CCL20 (previously known as macrophage inflammatory protein-3α

☆ All authors contributed equally to the writing of this chapter.

* *Corresponding author at:* Immunology Program, Department of Pathology, University of Michigan Medical School, 4701 BSRB, 109 Zina Pitcher Place, Ann Arbor, MI 48109-2200, USA. Fax: +1 734 764 2397.
E-mail address: slkunkel@umich.edu (S.L. Kunkel).

Abbreviations: APC, antigen presenting cell; DC, dendritic cell; Th, T-helper

0014-4827/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.yexcr.2010.12.018

or MIP-3α) [3,4]. CCL20 is expressed by a variety of epithelial cell types including keratinocytes, pulmonary epithelial cells, and intestinal epithelial cells [5–8] (Table 1). CCL20 is typically expressed at a low basal level, but can be strongly induced by pro-inflammatory signals including primary cytokines (e.g., TNF-α) and Toll-like receptor (TLR) agonists originating from microbes [9]. The production of CCL20 by human bronchial epithelial cells is regulated by the pro-inflammatory cytokines TNF-α and IL-1β, and also by pro-allergic cytokines IL-4 and IL-13, that are known to influence CCL20 expression by activation of both ERK1/2 and p38 MAPK pathways [8].

In addition to chemokine CCL20, non-chemokine human β-defensins-1 and -2 can also function as ligands for human CCR6 [10,11]. Relatedly, mouse β-defensins-2 and -3 can also serve as ligands for mouse CCR6 [12]. However, these β-defensins have lower affinities for CCR6 than for CCL20 [11]. For example, in vitro migration of $CD34^+$ progenitor-derived DCs is dose-dependent, with optimal concentrations of β-defensins at ~1000 ng/ml and of CCL20 at ~100 ng/ml. To date, the functional aspects of CCR6 binding to β-defensins remain unknown [4].

Mice lacking the CCR6 chemokine receptor ($CCR6^{-/-}$ mice) have demonstrated important roles for CCR6 in various lung and gut disease models. Understanding how defects in this specific chemokine receptor pathway alter immune responsiveness provides a valuable perspective for further defining the importance of CCR6 to the initiation and maintenance of immune/inflammatory responses. What follows is a review of the current knowledge regarding the role of CCR6 as a mediator of innate immunity in gut and lung mucosal sites.

Cell types expressing CCR6

The human CCR6 gene is located on chromosome 6q27 and the mouse CCR6 gene is located on chromosome 17 [13]. CCR6 is expressed on immature DCs [5,6,14,15], most B cells [16,17], subsets of $CD4^+$ and $CD8^+$ T cells [18], and NKT cells [19] (Table 2). Additionally, CCR6 is expressed by both central memory and effector memory T cells that are characterized by CCR7 expression [20,21]. While central memory T cells express CCR7 ($CD45RO^{high}$, $CCR6^+$, and $CCR7^+$), effector memory T cells do not ($CD45RO^{high}$, $CCR6^+$, and $CCR7^-$). CCR7 also is involved in organizing thymic architecture and function, lymph node homing of naive and regulatory T cells via high endothelial venules, and steady state and inflammation-induced lymph node-bound migration of DCs via afferent lymphatics [21].

Recent studies have also shown that CCR6 is a specific marker for Th17 cells and regulatory T cells distinguishing them from other helper T cells [22,23]. Interestingly, CCR6 is also expressed on some cancer cells [24,25], however the functionality on cancer cells is not clear. CCR6 expression has been reported on multiple

Table 1 – CCL20-expressing cells in the naïve state.

Cell types	References
Epithelial cells in the intestine	[6]
Follicule-associated epithelial (FAE) cell in Payer Patch	[14]
Epidermal keratinocyte	[5,7]
Venular endothelial cell	[5,7]
Epithelial crypts of tonsils	[56]
Pancreatic cancer cell	[25]
(Oral) squamous cell carcinoma	[57]

Table 2 – CCR6-expressing cells.

Cell types	Species	References
CD45RO+ memory T cell	Human	[18]
Th17 cell	Human, mouse	[22]
Regulatory T cell	Human, mouse	[23]
Naïve B cell	Human, mouse	[15,16]
Memory B cell	Human, mouse	[15,17]
CD11b+ CD8a− myeloid DC	Mouse	[6,15]
Immature CD34+ BM cell-derived myeloid DC	Human	[3,14]
Immature monocyte-derived DC	Human	[26]
Langerhans cell (LC)	Human	[5]
(Peritoneal) macrophage	Mouse	[28]
NKT cell	Human	[19]
HTLV-1 infected T cell	Human	[24]
Pancreatic cancer cell	Human	[25]

DC subsets including $CD11b^+CD8\alpha^-$ myeloid DCs [6,15], Langerhans cells (LC) [5], $CD34^+$ cell-derived immature myeloid DCs [3,14], and immature monocyte-derived DCs [26]. However, CCR6 is not expressed by $CD8\alpha^+$DC in mice [15]. DCs represent the most potent class of APCs in the immune system with the unique ability to induce primary immune responses against invading pathogens [27,28], suggesting that DCs are a key leukocyte population involved in driving the innate immune response.

There are several ways to induce DCs in an in vitro setting. For example, in the presence of GM-CSF + TNF-α, bone marrow-derived $CD34^+$ cells differentiate into $CCR6^+$ immature DCs [3,14]. CCR6 negative DCs are also induced by GM-CSF + IL-4 from monocytes in peripheral blood, while CCR6 expression requires the addition of TGF-β [26], suggesting that TGF-β is essential for the maintenance of an immature state. Immature DCs express various chemokine receptors such as CCR1, CCR2, CCR3, CCR5, CCR6, and CXCR4 [21,29,30]. However, CCR6 plays a non-redundant role in the induction of DC migration towards the epithelial layer of mucosal sites when pathogens and antigens invade peripheral tissues. Once immature DCs take up antigens in mucosal tissues, these DCs gain a mature status by down-regulating CCR6 expression, and by upregulating the expression of CCR7 [31]. Post-antigen uptake, DCs home to regional lymph nodes through afferent lymphatic vessels via the interaction of CCR7 with its ligands, CCL21/SLC and/or CCL19/ELC. Upon arrival in the regional lymph node, the mature DCs become effective APCs [31,32] (Fig. 1).

CCR6 in lung immunity

The presence of conventional and plasmocytoid DC subsets in so many lung compartments including airway epithelium, lung parenchyma, visceral pleura, and the bronchoalveolar space, attest to their importance in maintaining respiratory health [33]. In comparison to other lung compartments, immature DCs are highly abundant in human lung parenchyma where they express low levels of costimulatory molecules CD80 and CD86, actively display antigen uptake properties, and constitutively express chemokine receptors CCR1 and CCR5. These characteristics are hallmarks of immature DCs [34]. DCs are constantly recruited into the lungs, where they recognize inhaled antigens which transform them into APCs that migrate to the draining pulmonary lymph nodes where they activate antigen specific $CD4^+$ and $CD8^+$ T cells.

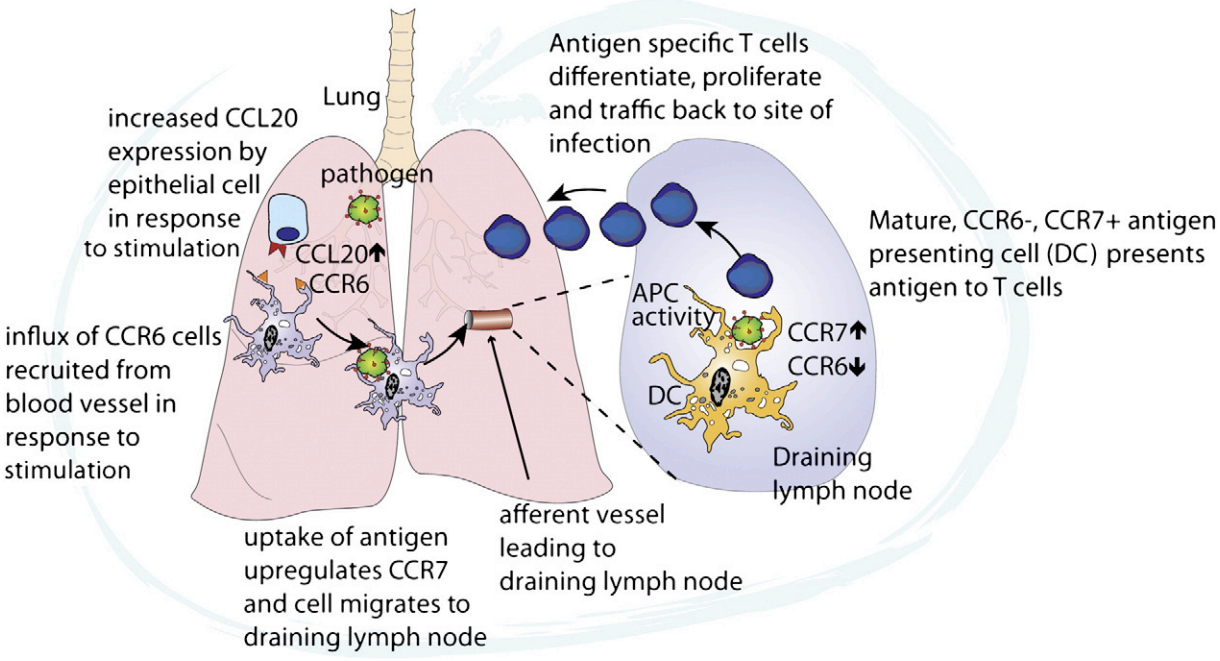


Fig. 1 – Blood born immature DCs traffic to the lung via the CCR6/CCL20 axis and take up antigen, and thus in the lung DCs mature and lose CCR6 expression while gaining the expression of CCR7. Post-antigen uptake, the DCs home to regional lymph nodes through afferent lymphatic vessels via the CCR7/CCL21 axis, where the mature DCs serve as an antigen presenting cell to lymphocytes.

Many cells in the lung produce a wide array of chemokines, which orchestrate the recruitment of DCs into the lung according to the stimulus present. For example, during pathogen infection of the lung, epithelial cells increase their production of CCL20 which in turn causes a further recruitment of immature $CCR6^+$ DCs into the lung (Fig. 1). Further, CCR6 is down-regulated during the maturation process as DCs migrate to the lymph node to fulfill its APC function, thus CCR6 is a chemokine specific to immature DCs. [5,14]. Various cytokines have been shown to regulate CCR6 expression in lung DCs. Regamey and collaborators showed that airway epithelial exposed to inflammatory cytokines IL-1β, TNF-α and IFN-γ produce IL-15, which cause monocytes to differentiate into partially mature DCs ($CCR6^+$ $CCR7^-$) that have characteristics of plasmocytoid DCs ($CD123^+$, $BDCA2^+$, $BDCA4^+$, $BDCA1^-$, and $CD1a^+$) [35]. Also, plasmocytoid DCs express high levels of CCR6 in melanoma patients [36]. These results belie the dogma that CCR6 expression is restricted to conventional DCs, and raise the question as to whether the expression of $CCR6^+$ on these non-conventional DCs might be important in specific pathologies.

The role of CCR6 has been explored in several allergic diseases. In a model of allergic airway inflammation induced by cockroach allergen in CCR6 deficient and CCR6 normal mice, the authors demonstrated that high levels of CCL20 are released within hours after allergen challenge and directly regulates the recruitment of conventional DCs into lung and subsequent T cell activation in a Th2 dependent manner [37]. During pulmonary Respiratory Syncial Virus (RSV) infection, the neutralization of CCL20 or CCR6-gene deficiency leads to increased viral clearance, that was directly dependent on the migration of conventional and not plasmocytoid DCs. Interestingly, RSV infection in CCR6-deficient mice generated a Th1-dominant response that contributed to interferon gamma (IFN-γ) production and the viral clearance. These data suggest that a pathogenic Th2 response is dictated by CCR6/CCL20 dependent recruitment of conventional DCs to the lung [38].

In a model of invasive pulmonary aspergillosis in immunocompromised mice (via transient antibody-mediated neutrophil depletion), $CD11c^+CD11b^{high}$ DCs expressing CCR6 accumulated in the lungs and these cells were necessary for effective host defense in neutropenic hosts, as CCR6-deficient mice developed severe infection and had higher mortality rate than WT controls [39]. Additionally, the recruitment of DC mediated by CCL20 was shown in the airways of patients with chronic obstructive pulmonary disease (COPD) suggesting that this receptor has an important role in chronic airway inflammation [40,41]. Increased CCL20 expression in patients with COPD compared to healthy controls was demonstrated by both RNA and protein levels in different compartments of the human lung [14,40]. Also, freshly isolated human pulmonary DCs from COPD patients appear to express CCR6. These observed correlations between the presence of chemokine CCL20 and the recruitment of $CCR6^+$ DCs to the lung, with lung pathogenesis in COPD suggest a possible mechanism for the increased influx of DCs into the airways in COPD. However, in CCR6-deficient mice exposed to cigarette smoke, an attenuated accumulation of several immune cells types including DCs, neutrophils and T cells in the lungs was observed. The authors implied that it was the attenuated migration of DCs that was most responsible for the protection from alveolar destruction and emphysema since these cells are the main source of matrix metalloproteinase-12 which causes progressive lung destruction in response to cigarette smoke [41].

In contrast to the above results in allergic, viral and fibrotic disease models, in models using antigens from *Mycobacteria bovis* and *Shistosoma mansoni*, DC recruitment to the lung was decreased

and lung DCs did not express CCR6 [42]. Indeed, transcripts of CCR6 were not observed in lung DCs in either model, and further, CCR6-deficient mice showed normal migration of DCs into infected lungs [42]. In both the *M. bovis* and *S. mansoni* models, the expression of CCR6 in DC populations was restricted to draining lung lymph nodes, suggesting that CCR6 has a role in the interactions between T cells. Further research is required to understand how CCR6 is regulated. Thus far, CCR6 expression in lung DCs is known to be transient and dependent on the microenvironment but other factors probably have a role as well.

Many chemokines are known to be involved in cancer metastases and tumorigenesis including CCR6 in lung cancer [43,44]. While investigations into the role of CCR6 in lung cancer are still in their infancy, a recent study showed that among the chemokine receptors analyzed (CX3CR1, CXCR4, CCR6, and CCR7), CCR6 and its ligand CCL20 are highly expressed in cancerous adrenal tissues that developed lung metastases when compared with primary tumors that did not metastasize [43]. CCL20 production in adrenal glands suggests that this chemokine contributes to the metastasis of CCR6-expressing tumor cells to the lung. On the contrary, in a mouse model of lung cancer (Lewis Lung Carcinoma, LLC), the expression of CCR6 by tumor cells was found to decrease the metastatic potential of these cells [44]. Thus, these findings open new therapeutic possibilities targeting CCL20/CCR6 axis in the metastasis of lung cancer.

CCR6 in gut immunity

The CCR6/CCL20 axis plays an important role in intestinal immunity. During normal development and immune homeostasis, CCR6-mediated signals help to organize lymphoid tissues such as Peyer's patches (PPs), mesenteric lymph nodes (MLNs) and gut-associated lymphoid tissue (GALT) by recruiting lymphoid and myeloid cells, including DCs and macrophages. In addition, CCR6-mediated signals are central to innate immune responses to normal intestinal flora, and modulations in CCR6 signals can have a significant impact on gut inflammatory responses to tissue damage and trauma. The relative CCR6-dependent chemotactic response of DCs and macrophages, and subsequent activation and effector function of these cell populations, plays an important role in intestinal immune responses.

As with other tissues, CCR6-mediated signals are critical for the organization of lymphoid tissues and the maintenance of leukocytes at sites critical for immune surveillance. In the gut, areas of secondary lymphoid organogenesis, such as PPs, isolated lymphoid follicles (ILFs), MLNs, and GALT show constitutive expression of CCL20, important for the chemotaxis of immature DCs [45]. In addition, expression of CCL20 (both mRNA and protein) can be induced in the follicle-associated epithelium (FAE) common to ILFs and PPs by organogenesis signals (such as lymphotoxin-beta signaling) [46]. CCL20 can also be induced in other intestinal epithelial cells in response to infection, in particular through LPS stimulation [47]; in this way, CCR6/CCL20 mediated signals can induce chemotaxis of CCR6-expressing dendritic cells and macrophages to sites of infection to help participate in the immune response.

Loss of CCR6/CCL20 signals can have a profound impact on innate immune cells in both the intestine and the peritoneal cavity. For example, $CCR6^{-/-}$ mice exhibit significant reductions in both DC and macrophage populations (both of which are myeloid lineage cells) in the peritoneal cavity, with no significant modulation in other lymphoid populations [28]. These results suggest that CCR6-mediated signals may play a more critical role in myeloid recruitment to the intestine (as compared to lymphoid recruitment) during homeostasis. The role of CCR6 in the organization of lymphoid structures in the intestinal mucosa may extend past the myeloid compartment as well; recent studies indicate that lineage-negative lymphoid tissue inducer cells in gut cryptopatches (CPs) express CCR6, and $CCR6^{-/-}$ mice exhibit inhibition of cryptopatch formation [48]. The CCR6/CCL20 axis is not the only chemotactic pathway for DCs in the intestine; for example, CCL9 can also recruit DCs to the subepithelial dome [49]. However, it is clear that CCR6-mediated signals can play a role in the maintenance of DC and macrophage populations throughout the intestinal mucosa.

In addition to its role in gut homeostasis, CCR6-mediated signals are also essential for immune responses to microbes and microbial products in the intestinal mucosa. For example, $CCR6^{-/-}$ mice have impaired antibody responses to both oral immunizations and mucosal virus infections; interestingly, this reduction in antibody production appears localized to the gut, as systemic antibody levels are not perturbed in $CCR6^{-/-}$ mice in these models [50]. $CCR6^{+}$ DCs in the subepithelial dome (SED) also appear to be critical for the activation and proliferation of $CD4^{+}$ T cells at the site of infection in murine models of enteric pathogen infection, as CCR6-expressing T cells were reduced in number in LNs and PPs during infection when transferred into CCR6-deficient hosts [51]. In addition, $CCR6^{+}$ DCs are recruited to the FAE of PPs in response to bacterial infection, suggesting that CCR6/CCL20 signals are critical both for homeostasis and active inflammation [51]. CCR6 can also modulate harmful inflammatory processes in the gut, as shown in the $CCR6^{-/-}$ mouse model with inflammatory bowel disease (IBD) [52]. Interestingly, the observed pathology of CCR6-deficient IBD models depends on the agent used; while dextran sodium sulfate (DSS)—induced IBD is less severe in $CCR6^{-/-}$ mice, trinitrobenzene sulfonic acid (TNBS)-induced IBD is more severe, as compared to wild-type mice [52]. The observed differences in disease severity may be a reflection of the modulation of leukocyte populations in the intestine as a result of CCR6 deficiency, as DSS- and TNBS-induced colitis is thought to occur via differing mechanisms (myeloid non-specific inflammation vs. lymphoid antigen-driven inflammation, respectively) [52].

CCR6 also plays an important role in the modulation of inflammatory responses initiated by tissue insult and trauma. For example, CCL20 is induced by bateria-induced peritonitis, and $CCR6^{-/-}$ mice are resistant to peritonitis-induced mortality in a surgical model of severe sepsis [28]. Interestingly, this protection appears to be due to mechanisms beyond leukocyte migration to the intestinal mucosa. While $CCR6^{-/-}$ mice do exhibit reductions in both macrophages and DCs in the peritoneal cavity, $CCR6^{-/-}$ macrophages exhibit reduced inflammatory responses to LPS stimulation *in vitro*, as evidenced by cytokine production [28]. Additionally, $CCR6^{-/-}$ mice exhibit reduced cytokine and chemokine levels in the peritoneal cavity during acute peritonitis, suggesting that the reduced sepsis-induced mortality may be due to the impaired pro-inflammatory capacity of immune cells lacking $CCR6^{-/-}$. These results suggest that CCR6-mediated signals in macrophages and DCs may be important for cell activation during exposure to microbes and/or microbial products;

however, the specific mechanistic link governing the connection between microbial products and CCR6-mediated signals, for example, remains unknown.

Conclusion

The contribution of CCR6 binding to its chemokine ligand, CCL20, has been demonstrated to participate in a number of lung and gut disorders, ranging from asthma and COPD to IBD. In these tissue settings, CCR6 has been identified as an important receptor which is involved in regulating multiple aspects of mucosal immunity, including the ability to mediate the recruitment of immature DCs and mature DCs, APCs, to the sites of epithelial inflammation and homing of both $CD4^+$ T (T-helper; Th) cells and DCs to mucosal lymphoid tissue. DCs, which are known to be essential immune cells in innate immunity and in the initiation of adaptive immunity, play a central role in the initiation and maintenance of the primary immune response. Interestingly, accumulating evidence supports the view that the CCR6/CCL20 axis also plays an important role in other pathologies that include cancer and autoimmune diseases [23,53]. For example, CCR6 is expressed in several cancer types such as lung cancer, colorectal cancer, and pancreatic cancer where CCR6/CCL20 interactions have been reported to promote cancer cell proliferation and migration. In fact, human tumor vaccines that target DCs are considered by many as the vaccine strategy of the future and have been tested in clinical trials [54,55]. There is little doubt that a more complete understanding of the role of chemokine/chemokine receptor axis in various disorders will lead to therapeutic applications for a variety of human inflammatory diseases.

Acknowledgments

This work was supported by NIH grants HL31237, HL89216, HL92845, and HL31963. We thank Robin Kunkel for her artistic work.

REFERENCES

[1] D. Rossi, A. Zlotnik, The biology of chemokines and their receptors, Annu. Rev. Immunol. 18 (2000) 217–242.
[2] O. Yoshie, T. Imai, H. Nomiyama, Chemokines in immunity, Adv. Immunol. 78 (2001) 57–110.
[3] C.A. Power, D.J. Church, A. Meyer, S. Alouani, A.E. Proudfoot, I. Clark-Lewis, S. Sozzani, A. Mantovani, T.N. Wells, Cloning and characterization of a specific receptor for the novel CC chemokine MIP-3alpha from lung dendritic cells, J. Exp. Med. 186 (1997) 825–835.
[4] I.R. Williams, Chemokine receptors and leukocyte trafficking in the mucosal immune system, Immunol. Res. 29 (2004) 283–292.
[5] A.S. Charbonnier, N. Kohrgruber, E. Kriehuber, G. Stingl, A. Rot, D. Maurer, Macrophage inflammatory protein 3alpha is involved in the constitutive trafficking of epidermal Langerhans cells, J. Exp. Med. 190 (1999) 1755–1768.
[6] A. Iwasaki, B.L. Kelsall, Localization of distinct Peyer's patch dendritic cell subsets and their recruitment by chemokines macrophage inflammatory protein (MIP)-3alpha, MIP-3beta, and secondary lymphoid organ chemokine, J. Exp. Med. 191 (2000) 1381–1394.
[7] T. Nakayama, R. Fujisawa, H. Yamada, T. Horikawa, H. Kawasaki, K. Hieshima, D. Izawa, S. Fujiie, T. Tezuka, O. Yoshie, Inducible expression of a CC chemokine liver- and activation-regulated chemokine (LARC)/macrophage inflammatory protein (MIP)-3 alpha/CCL20 by epidermal keratinocytes and its role in atopic dermatitis, Int. Immunol. 13 (2001) 95–103.
[8] J. Reibman, Y. Hsu, L.C. Chen, B. Bleck, T. Gordon, Airway epithelial cells release MIP-3alpha/CCL20 in response to cytokines and ambient particulate matter, Am. J. Respir. Cell Mol. Biol. 28 (2003) 648–654.
[9] E. Schutyser, S. Struyf, J. Van Damme, The CC chemokine CCL20 and its receptor CCR6, Cytokine Growth Factor Rev. 14 (2003) 409–426.
[10] M. Baba, T. Imai, M. Nishimura, M. Kakizaki, S. Takagi, K. Hieshima, H. Nomiyama, O. Yoshie, Identification of CCR6, the specific receptor for a novel lymphocyte-directed CC chemokine LARC, J. Biol. Chem. 272 (1997) 14893–14898.
[11] D. Yang, O. Chertov, S.N. Bykovskaia, Q. Chen, M.J. Buffo, J. Shogan, M. Anderson, J.M. Schroder, J.M. Wang, O.M. Howard, J.J. Oppenheim, Beta-defensins: linking innate and adaptive immunity through dendritic and T cell CCR6, Science 286 (1999) 525–528.
[12] A. Biragyn, M. Surenhu, D. Yang, P.A. Ruffini, B.A. Haines, E. Klyushnenkova, J.J. Oppenheim, L.W. Kwak, Mediators of innate immunity that target immature, but not mature, dendritic cells induce antitumor immunity when genetically fused with nonimmunogenic tumor antigens, J. Immunol. 167 (2001) 6644–6653.
[13] F. Liao, H.H. Lee, J.M. Farber, Cloning of STRL22, a new human gene encoding a G-protein-coupled receptor related to chemokine receptors and located on chromosome 6q27, Genomics 40 (1997) 175–180.
[14] D.R. Greaves, W. Wang, D.J. Dairaghi, M.C. Dieu, B. Saint-Vis, K. Franz-Bacon, D. Rossi, C. Caux, T. McClanahan, S. Gordon, A. Zlotnik, T.J. Schall, CCR6, a CC chemokine receptor that interacts with macrophage inflammatory protein 3alpha and is highly expressed in human dendritic cells, J. Exp. Med. 186 (1997) 837–844.
[15] T. Kucharzik, J.T. Hudson III, R.L. Waikel, W.D. Martin, I.R. Williams, CCR6 expression distinguishes mouse myeloid and lymphoid dendritic cell subsets: demonstration using a CCR6 EGFP knock-in mouse, Eur. J. Immunol. 32 (2002) 104–112.
[16] E.P. Bowman, J.J. Campbell, D. Soler, Z. Dong, N. Manlongat, D. Picarella, R.R. Hardy, E.C. Butcher, Developmental switches in chemokine response profiles during B cell differentiation and maturation, J. Exp. Med. 191 (2000) 1303–1318.
[17] R. Krzysiek, E.A. Lefevre, J. Bernard, A. Foussat, P. Galanaud, F. Louache, Y. Richard, Regulation of CCR6 chemokine receptor expression and responsiveness to macrophage inflammatory protein-3alpha/CCL20 in human B cells, Blood 96 (2000) 2338–2345.
[18] F. Liao, R.L. Rabin, C.S. Smith, G. Sharma, T.B. Nutman, J.M. Farber, CC-chemokine receptor 6 is expressed on diverse memory subsets of T cells and determines responsiveness to macrophage inflammatory protein 3 alpha, J. Immunol. 162 (1999) 186–194.
[19] C.H. Kim, B. Johnston, E.C. Butcher, Trafficking machinery of NKT cells: shared and differential chemokine receptor expression among V alpha 24(+)V beta 11(+) NKT cell subsets with distinct cytokine-producing capacity, Blood 100 (2002) 11–16.
[20] F. Sallusto, A. Lanzavecchia, Understanding dendritic cell and T-lymphocyte traffic through the analysis of chemokine receptor expression, Immunol. Rev. 177 (2000) 134–140.
[21] R. Förster, A.C. Davalos-Misslitz, A. Rot, CCR7 and its ligands: balancing immunity and tolerance, Nat. Rev. Immunol. 8 (2008) 362–371.
[22] K. Hirota, H. Yoshitomi, M. Hashimoto, S. Maeda, S. Teradaira, N. Sugimoto, T. Yamaguchi, T. Nomura, H. Ito, T. Nakamura, N. Sakaguchi, S. Sakaguchi, Preferential recruitment of CCR6-expressing Th17 cells to inflamed joints via CCL20 in rheumatoid arthritis and its animal model, J. Exp. Med. 204 (2007) 2803–2812.

[23] M. Kleinewietfeld, F. Puentes, G. Borsellino, L. Battistini, O. Rötzschke, F. Kirsten, CCR6 expression defines regulatory effector/memory-like cells within the CD25+CD4+ T-cell subset, Blood 105 (2005) 2877–2886.
[24] Y. Imaizumi, S. Sugita, K. Yamamoto, D. Imanishi, T. Kohno, M. Tomonaga, T. Matsuyama, Human T cell leukemia virus type-I Tax activates human macrophage inflammatory protein-3 alpha/CCL20 gene transcription via the NF-kappa B pathway, Int. Immunol. 14 (2002) 147–155.
[25] J. Kleeff, T. Kusama, D.L. Rossi, T. Ishiwata, H. Maruyama, H. Friess, M.W. Buchler, A. Zlotnik, M. Korc, Detection and localization of Mip-3alpha/LARC/Exodus, a macrophage proinflammatory chemokine, and its CCR6 receptor in human pancreatic cancer, Int. J. Cancer 81 (1999) 650–657.
[26] D. Yang, O.M. Howard, Q. Chen, J.J. Oppenheim, Cutting edge: immature dendritic cells generated from monocytes in the presence of TGF-beta 1 express functional C-C chemokine receptor 6, J. Immunol. 163 (1999) 1737–1741.
[27] J. Banchereau, R.M. Steinman, Dendritic cells and the control of immunity, Nature 392 (1998) 245–252.
[28] H. Wen, C.M. Hogaboam, N.W. Lukacs, D.N. Cook, S.A. Lira, S.L. Kunkel, The chemokine receptor CCR6 is an important component of the innate immune response, Eur. J. Immunol. 37 (2007) 2487–2498.
[29] M.C. Dieu, B. Vanbervliet, A. Vicari, J.M. Bridon, E. Oldham, S. Ait-Yahia, F. Briere, A. Zlotnik, S. Lebecque, C. Caux, Selective recruitment of immature and mature dendritic cells by distinct chemokines expressed in different anatomic sites, J. Exp. Med. 188 (1998) 373–386.
[30] K. Sato, H. Kawasaki, H. Nagayama, M. Enomoto, C. Morimoto, K. Tadokoro, T. Juji, T.A. Takahashi, TGF-beta 1 reciprocally controls chemotaxis of human peripheral blood monocyte-derived dendritic cells via chemokine receptors, J. Immunol. 164 (2000) 2285–2295.
[31] M.C. Dieu-Nosjean, A. Vicari, S. Lebecque, C. Caux, Regulation of dendritic cell trafficking: a process that involves the participation of selective chemokines, J. Leukoc. Biol. 66 (1999) 252–262.
[32] H. Saeki, A.M. Moore, M.J. Brown, S.T. Hwang, Cutting edge: secondary lymphoid-tissue chemokine (SLC) and CC chemokine receptor 7 (CCR7) participate in the emigration pathway of mature dendritic cells from the skin to regional lymph nodes, J. Immunol. 162 (1999) 2472–2475.
[33] V.S. Donnenberg, A.D. Donnenberg, Identification, rare-event detection and analysis of dendritic cell subsets in broncho-alveolar lavage fluid and peripheral blood by flow cytometry, Front. Biosci. 8 (2003) s1175–s1180.
[34] L. Cochand, P. Isler, F. Songeon, L.P. Nicod, Human lung dendritic cells have an immature phenotype with efficient mannose receptors, Am. J. Respir. Cell Mol. Biol. 21 (1999) 547–554.
[35] N. Regamey, C. Obregon, S. Ferrari-Lacraz, C. van Leer, M. Chanson, L.P. Nicod, T. Geiser, Airway epithelial IL-15 transforms monocytes into dendritic cells, Am. J. Respir. Cell Mol. Biol. 37 (2007) 75–84.
[36] J. Charles, J. Di Domizio, D. Salameire, N. Bendriss-Vermare, C. Aspord, R. Muhammad, C. Lefebvre, J. Plumas, M.T. Leccia, L. Chaperot, Characterization of circulating dendritic cells in melanoma: role of CCR6 in plasmacytoid dendritic cell recruitment to the tumor, J Invest Dermatol 130 (2010) 1646–1656.
[37] S.K. Lundy, S.A. Lira, J.J. Smit, D.N. Cook, A.A. Berlin, N.W. Lukacs, Attenuation of allergen-induced responses in CCR6−/− mice is dependent upon altered pulmonary T lymphocyte activation, J. Immunol. 174 (2005) 2054–2060.
[38] L.E. Kallal, M.A. Schaller, D.M. Lindell, S.A. Lira, N.W. Lukacs, CCL20/CCR6 blockade enhances immunity to RSV by impairing recruitment of DC, Eur J Immunol 40 (2010) 1042–1052.
[39] A.P. Phadke, G. Akangire, S.J. Park, S.A. Lira, B. Mehrad, The role of CC chemokine receptor 6 in host defense in a model of invasive pulmonary aspergillosis, Am. J. Respir. Crit. Care Med. 175 (2007) 1165–1172.
[40] I.K. Demedts, K.R. Bracke, G. Van Pottelberge, D. Testelmans, G.M. Verleden, F.E. Vermassen, G.F. Joos, G.G. Brusselle, Accumulation of dendritic cells and increased CCL20 levels in the airways of patients with chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care Med. 175 (2007) 998–1005.
[41] K.R. Bracke, I. D'Hulst, A.T. Maes, K.B. Moerloose, I.K. Demedts, S. Lebecque, G.F. Joos, G.G. Brusselle, Cigarette smoke-induced pulmonary inflammation and emphysema are attenuated in CCR6-deficient mice, J. Immunol. 177 (2006) 4350–4359.
[42] B.C. Chiu, C.M. Freeman, V.R. Stolberg, J.S. Hu, K. Zeibecoglou, B. Lu, C. Gerard, I.F. Charo, S.A. Lira, S.W. Chensue, Impaired lung dendritic cell activation in CCR2 knockout mice, Am. J. Pathol. 165 (2004) 1199–1209.
[43] C.M. Raynaud, O. Mercier, P. Dartevelle, F. Commo, K.A. Olaussen, V. de Montpreville, F. Andre, L. Sabatier, J.C. Soria, Expression of chemokine receptor CCR6 as a molecular determinant of adrenal metastatic relapse in patients with primary lung cancer, Clin Lung Cancer 11 (2010) 187–191.
[44] A. Sutherland, J.F. Mirjolet, A. Maho, M. Parmentier, Expression of the chemokine receptor CCR6 in the Lewis lung carcinoma (LLC) cell line reduces its metastatic potential in vivo, Cancer Gene Ther. 14 (2007) 847–857.
[45] P. Anderle, M. Rumbo, F. Sierro, R. Mansourian, P. Michetti, M.A. Roberts, J.P. Kraehenbuhl, Novel markers of the human follicle-associated epithelium identified by genomic profiling and microdissection, Gastroenterology 129 (2005) 321–327.
[46] M. Rumbo, F. Sierro, N. Debard, J.P. Kraehenbuhl, D. Finke, Lymphotoxin beta receptor signaling induces the chemokine CCL20 in intestinal epithelium, Gastroenterology 127 (2004) 213–223.
[47] S. Fujiie, K. Hieshima, D. Izawa, T. Nakayama, R. Fujisawa, H. Ohyanagi, O. Yoshie, Proinflammatory cytokines induce liver and activation-regulated chemokine/macrophage inflammatory protein-3alpha/CCL20 in mucosal epithelial cells through NF-kappaB [correction of NK-kappaB], Int. Immunol. 13 (2001) 1255–1263.
[48] A. Lugering, M. Ross, M. Sieker, J. Heidemann, I.R. Williams, W. Domschke, T. Kucharzik, CCR6 identifies lymphoid tissue inducer cells within cryptopatches, Clin. Exp. Immunol. 160 (2010) 440–449.
[49] X. Zhao, A. Sato, C.S. Dela Cruz, M. Linehan, A. Luegering, T. Kucharzik, A.K. Shirakawa, G. Marquez, J.M. Farber, I. Williams, A. Iwasaki, CCL9 is secreted by the follicle-associated epithelium and recruits dome region Peyer's patch CD11b+ dendritic cells, J. Immunol. 171 (2003) 2797–2803.
[50] D.N. Cook, D.M. Prosser, R. Forster, J. Zhang, N.A. Kuklin, S.J. Abbondanzo, X.D. Niu, S.C. Chen, D.J. Manfra, M.T. Wiekowski, L.M. Sullivan, S.R. Smith, H.B. Greenberg, S.K. Narula, M. Lipp, S.A. Lira, CCR6 mediates dendritic cell localization, lymphocyte homeostasis, and immune responses in mucosal tissue, Immunity 12 (2000) 495–503.
[51] R.M. Salazar-Gonzalez, J.H. Niess, D.J. Zammit, R. Ravindran, A. Srinivasan, J.R. Maxwell, T. Stoklasek, R. Yadav, I.R. Williams, X. Gu, B.A. McCormick, M.A. Pazos, A.T. Vella, L. Lefrancois, H.C. Reinecker, S.J. McSorley, CCR6-mediated dendritic cell activation of pathogen-specific T cells in Peyer's patches, Immunity 24 (2006) 623–632.
[52] R. Varona, V. Cadenas, J. Flores, A.C. Martinez, G. Marquez, CCR6 has a non-redundant role in the development of inflammatory bowel disease, Eur. J. Immunol. 33 (2003) 2937–2946.
[53] G. Page, S. Lebecque, P. Miossec, Anatomic localization of immature and mature dendritic cells in an ectopic lymphoid organ: correlation with selective chemokine expression in rheumatoid synovium, J. Immunol. 168 (2002) 5333–5341.
[54] P. Ghadjar, C. Rubie, D.M. Aebersold, U. Keilholz, The chemokine CCL20 and its receptor CCR6 in human malignancy with focus on colorectal cancer, Int. J. Cancer 125 (2009) 741–745.

[55] T.R. Petersen, N. Dickgreber, I.F. Hermans, Tumor antigen presentation by dendritic cells, Crit. Rev. Immunol. 30 (2010) 345–386.
[56] M. Casamayor-Palleja, P. Mondiere, A. Amara, C. Bella, M.C. Dieu-Nosjean, C. Caux, T. Defrance, Expression of macrophage inflammatory protein-3alpha, stromal cell-derived factor-1, and B-cell-attracting chemokine-1 identifies the tonsil crypt as an attractive site for B cells, Blood 97 (2001) 3992–3994.
[57] Y. Abiko, M. Nishimura, K. Kusano, K. Nakashima, K. Okumura, T. Arakawa, T. Takuma, I. Mizoguchi, T. Kaku, Expression of MIP-3alpha/CCL20, a macrophage inflammatory protein in oral squamous cell carcinoma, Arch. Oral Biol. 48 (2003) 171–175.