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CXCL17 Is a Major Chemotactic Factor for Lung Macrophages

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Chemokines are a superfamily of chemotactic cytokines that direct the movement of cells throughout the body under homeostatic and inflammatory conditions. The mucosal chemokine CXCL17 was the last ligand of this superfamily to be characterized. Several recent studies have provided greater insight into the basic biology of this chemokine and have implicated CXCL17 in several human diseases. We sought to better characterize CXCL17’s activity in vivo. To this end, we analyzed its chemoattractant properties in vivo and characterized a Cxcl17−/− mouse. This mouse has a significantly reduced number of macrophages in its lungs compared with wild-type mice. In addition, we observed a concurrent increase in a new population of macrophage-like cells that are F4/80+CD11cmid. These results indicate that CXCL17 is a novel macrophage chemoattractant that operates in mucosal tissues. Given the importance of macrophages in inflammation, these observations strongly suggest that CXCL17 is a major regulator of mucosal inflammatory responses. The Journal of Immunology, 2014, 193: 1468–1474.

The immune system is a complex network of cell types that are widely disseminated throughout the body. Despite these long distances, the cells retain the ability to interact and communicate so they can mount effective immune responses. To accomplish this, cells of the immune system rely on the production of cytokines. A subset of these cytokines regulate the trafficking of immune cells in the body and are therefore called chemotactic cytokines, or chemokines.

The human chemokine superfamily includes 48 secreted ligands and 19 receptors (1–3). Chemokines have a distinctive three-dimensional structure, which relies on four conserved cysteine residues that form disulfide bonds. The distribution of these four cysteine molecules within the chemokine structure is the criterion used to divide the superfamily into subclasses: CC, CXC, CX3C, and XC (1–3). In addition to their role in the development of immune responses, some chemokines are also expressed under homeostatic conditions in specific tissues. Chemokines of this group, known as homeostatic chemokines, are important for directing the homing of subsets of immune cells into secondary and tertiary immune tissues (1, 2).

CXCL17 was the last chemokine ligand of the human chemokine superfamily to be described (4). Consequently, few reports describing the biology of CXCL17 are available. Several recent studies have documented a role for CXCL17 in tumor progression (5–9), inflammation (10), and human disease (11). These studies suggest that CXCL17 fulfills important physiological roles in vivo under both homeostatic and inflammatory conditions. Furthermore, these findings suggest that CXCL17 is an important player underlying the pathological conditions observed in these diseases. To gain a better understanding of CXCL17’s role in vivo, we sought to obtain and analyze a CXCL17-deficient (Cxcl17−/−) mouse.

Knockout mice are common research tools used to study chemokine biology. CXCR4- or CXCL12-deficient mice, for example, revealed that this receptor/ligand axis is critically involved in development (12–14). Similarly, mice lacking CCR7 expression pointed to a pivotal role of the CCL21/CCR7 axis in lymphocyte homing to lymph nodes (LNs) (15–18). Although these chemokines/receptors have been well characterized, their respective knockout mice were critical tools that aided in the characterization and understanding of their functional roles (15, 19–21). These observations underscore the importance of a given chemokine-deficient mouse in understanding its biology.

Human and mouse Cxcl17 share 71% sequence identity at the amino acid level (4). In addition, a similar pattern of CXCL17 expression in mucosal tissues of both human and corresponding murine tissues has been observed (4, 5, 9–11). Therefore, we predicted that a Cxcl17−/− mouse would provide us with important information about CXCL17’s in vivo activity. The remarkably similar CXCL17 expression patterns in both human and mouse suggest that the phenotype of a CXCL17-deficient mouse will mirror the biology of human CXCL17.

Prior to studying a Cxcl17−/− mouse, we wanted to gain further insight into CXCL17’s expression profile and in vivo chemotactic activity. Comparison of the gene expression profiles of Cxcl17 in germ-free (GF) and specific pathogen–free (SPF) mice established that CXCL17 exhibits both a homeostatic and an inflammatory expression profile, which classifies it as a “dual” chemokine (1–3). In line with previous in vitro chemotaxis studies, we were able to
demonstrate that in vivo, CXCL17 preferentially chemotractions macrophages, and, to a lesser extent, dendritic cells (DCs).

Given our previous findings of CXCL17’s robust expression in the lung and association with idiopathic pulmonary fibrosis (IPF) (11), we focused our phenotypic analysis on the lungs of Cxcl17+/- mice. Our findings indicate that Cxcl17+/- mice exhibit a paucity of macrophages in their lungs. Through population-specific analyses, we observed a significant reduction in the numbers of alveolar macrophages (AMs), but not interstitial macrophages (IMs), in Cxcl17+/- mice compared with wild-types (WTs). Of interest, we also observed a significant increase in a population of F4/80+CD11c-mid cells that have macrophage-like characteristics. Taken together, we conclude that CXCL17 is an important mucosal macrophage chemotactic factor.

Materials and Methods

**Mice**

Cxcl17+/- mice were obtained from the Knock Out Mouse Project at University of California, Davis (Genentech ID UNQ473). Cxcl17+/- mice were bred to generate Cxcl17+/- mice. WT mice for breeding purposes were purchased from The Jackson Laboratory (http://jaxmice.jax.org). All mice were housed in the same SPF facility with a 12-h dark/light cycle and were provided with a 10% FBS in 1× washed with 2 ml 1× CA). The Alexa Fluor 488 anti-mouse Gr-1 was used at a concentration of 0.25–1× 10⁶ cells, depending on total numbers of mice. All primary cells were collected from 3- to 6-wk-old WT female C57BL/6-B129 mice housed in an SPF facility. Spleenocytes were collected using manual dissociation followed by RBC lysis with ACK lysing buffer. Lung intraepithelial cells were collected by manual dissociation after a 1-h collagenase digestion at 37°C. Pleural and peritoneal cells were obtained by washing each respective cavity with sterile 1× PBS. No further processing of these cells was required prior to their use in the chemotaxis assay. All animal procedures were performed according to approved Institutional Animal Care and Use Committee protocols.

**Chemotaxis assays**

The chemotaxis assays were performed using 24-well Transwell migration plates (Corning, NY), which contain an upper insert and a lower chamber. A total of 200 ng recombinant chemokine (R&D Systems) in 600 μl chemotaxis buffer (incomplete RPMI; Mediatech, Manassas, VA) was added to the bottom chamber of the Transwell plate. The Transwell plates used in these assays had 5.0-μm pores. A total of 1.0 × 10⁶ cells were used as the input cell number for all cell lines tested, unless otherwise noted. Prior to their addition to the top insert assay plate, the cells were washed three times in chemotaxis buffer. The assay was incubated at 37°C and 5% CO₂ for 18–20 h. Chemotaxis was periodically monitored using a microscope.

**Quantification of chemotaxis by flow cytometry**

This protocol was adapted from Proudfoot et al. (22). Briefly, at the termination of the chemotaxis assay, the chemotaxed cells were collected from the bottom chamber of the plate, spun down in FACS tubes, and then resuspended in 200 μl 1× PBS. Standards were generated by making 10-fold dilutions of cells ranging from 1.0 × 10⁶ to 1.0 × 10⁴ cells in 200 μl 1× PBS. The cell counts for the standards and all of the chemotaxed cells were recorded as the number of events counted in 30 s. Because the precise number of cells was known for the standards, their cell counts were used to generate a standard curve. The trendline and equation resulting from this standard curve were used to calculate the relative number of cells that chemotaxed for each cell line or primary cell analyzed. A FACScanCalibur flow cytometer (Becton Dickinson) was used for these quantification experiments.

**QRT-PCR analysis**

Total RNA was extracted from mouse tissues using TRIzol (Invitrogen, Carlsbad, CA) and subsequently purified using RNaseasy columns and DNase digest (QIAGEN). Equal concentrations of RNA were used for each tissue sample in a reverse transcription reaction to synthesize cDNA (QIAGEN). Each reaction used 50 ng/ml of each cDNA, gene-specific primers, and gene-specific Universal ProbeLibrary probes to quantitatively detect Cxcl17 and control gene transcripts in each tissue sample. The results were processed in Excel and analyzed using GraphPad Prism (http://www.graphpad.com/).

**FACS staining of immune cell populations**

Spleen, LNs, bone marrow, and cells from peritoneal and pleural lavages, and lungs were collected from WT and Cxcl17+/- mice. Soluble organs were passed through 40-μm strainers rinsed with 1× PBS to make single-cell suspensions. A total of 0.25–1 × 10⁶ cells, depending on total numbers obtained from the organs, were transferred to FACS tubes. Fe receptors were blocked using blocking buffer (4% PBS in 1× PBS) and 0.1 μl unlabeled anti-CD16/32 (anti-Fc receptor). Screening of the macrophage/monocyte/DC populations was achieved by staining the cells with the following mixture: PerCP anti-mouse F4/80, Alexa 488 anti-mouse CD11c (iCyt, Champaign, IL), PE anti-mouse B220, and APC anti-mouse CD11b (iCyt). For all stainings, the Abs were used at 1:1000 in 1× PBS. The cell counts for the standards and all of the chemotaxed cells were recorded as the number of events counted in 30 s. Because the precise number of cells was known for the standards, their cell counts were used to generate a standard curve. The trendline and equation resulting from this standard curve were used to calculate the relative number of cells that chemotaxed for each cell line or primary cell analyzed. A FACScanCalibur flow cytometer (Becton Dickinson) and the data were analyzed using FlowJo software (TreeStar) and GraphPad Prism (http://www.graphpad.com/).

**Immunohistochemical staining of tissues**

Tissue sections from formalin-fixed, paraffin-embedded samples were selected from autopsy files for normal human bronchial mucosa. Two 5-mm tissue punches were taken from the relevant tissues and included in a paraffin block containing four different samples. Tissue sections were deparaffinized on siliconized slides, and xylol was used to remove the paraffin. The tissue sections were then rehydrated in ethanol solutions at progressively lower concentrations. Epitope retrieval was achieved by placing the tissue sections in a pressure cooker for 15 min.
The resulting slides were incubated with an anti-human CXCL17 Ab (R&D Systems) or an isotype control. The primary Ab was incubated in a polymer-based visualization kit (DAKO, Carpinteria, CA) for 10 min per the manufacturer’s instructions. The completed reaction was revealed with diaminobenzidine and counterstained with hematoxylin. Positive staining was evaluated and recorded by a pathologist.

**Results**

**CXCL17 is a dual chemokine (inflammatory and homeostatic)**

We and others (4, 5, 9–11) have previously profiled CXCL17’s expression in both humans and mice. These gene expression analyses have established that CXCL17 is highly expressed in mucosal tissues of the digestive and respiratory system as well as in the female reproductive tract (4, 5, 9–11).

Chemokines have been divided into three different expression groups: homeostatic, inflammatory, or dual, based on their expression patterns (1–3). The dual classification means that the ligand is expressed under both homeostatic and inflammatory conditions. In the case of CXCL17, its expression classification (homeostatic versus inflammatory) has yet to be established. To determine CXCL17’s expression characteristics and properly classify it, we analyzed the expression pattern of Cxcl17 in tissues from GF, SPF, and normally housed mice. SPF and mice housed in normal conditions will be colonized by “normal” microbial flora, and therefore will have a low level of inflammation at their mucosal sites as a result of this colonization (23–26); owing to their microbial sterility, the GF mice should not exhibit even basal inflammation at their mucosal surfaces. Therefore, CXCL17 expression in GF and SPF/normal mice should reflect the chemokine’s homeostatic and inflammatory expression profile at mucosal sites, respectively.

The expression of Cxcl17 in the mucosal tissues of these mice was determined using QRT-PCR (Fig. 1). In agreement with our previous observation in human and murine tissues, Cxcl17 is robustly expressed in the trachea, lung, and tongue, with lower expression detected in intestinal tissues. Within gut tissues, Cxcl17 expression is lower in the GF and SPF samples compared with normally housed mice. This trend is also observed in the stomach, tongue, and lung of the differentially housed mice. However, Cxcl17 expression in the trachea of GF and SPF mice was not significantly reduced compared with mice housed in a normal vivarium. These data indicate that in the trachea, CXCL17 is expressed under homeostatic conditions, but its expression under varying conditions in other mucosal tissues indicates that it is upregulated under inflammatory conditions. We conclude that CXCL17 is a dual (homeostatic/inflammatory) chemokine.

**CXCL17 preferentially chemoattracts macrophages in vivo**

Previous studies have analyzed CXCL17’s chemotactic activity via in vitro analyses (i.e., chemotaxis assays) (4, 6, 9). These assays are important tools for the initial studies of a chemokine’s chemotactic activities, but they may not always reflect its chemotactic activity under normal in vivo conditions. We therefore sought to analyze the chemotactic activity of CXCL17 in a more physiological context. To this end, we injected WT mice with Cxcl17 i.p., and the cellular contents of the peritoneal cavities were collected and analyzed by flow cytometry. As shown in Fig. 2 and Supplemental Fig. 1, the peritoneal cavities of mice injected with recombinant Cxcl17 contained significantly more F4/80+ CD11b+ macrophages by 24 h and 48 h than the cavities of mice that received PBS (Fig. 2). We observed no significant difference in the recruitment of DCs. It has been reported that CXCL17 recruits neutrophils (9), but we did not observe changes in the recruitment of these cells to the peritoneal cavity following Cxcl17 injection (data not shown). These data indicate that CXCL17 is a potent macrophage chemotactic factor in vivo.

**Phenotype of a Cxcl17-deficient mouse**

To gain further insight into the biology of CXCL17, we obtained a Cxcl17−/− mouse strain. These animals were cryo-recovered from the Mutant Mouse Regional Resource Center at University of California, Davis, Davis, California (27, 28). We obtained the animals following successful resuscitation, at which point the mice were heterozygous for the Cxcl17 deletion. The first of four exons was targeted via homologous recombination to inactivate the Cxcl17 gene on chromosome 7. Careful breeding and genotyping yielded Cxcl17−/− mice (Supplemental Fig. 2). Homozygous Cxcl17−/− mice show no defects in breeding or gross anatomy development, and they gained weight normally (data not shown).

Given that this is the first report to our knowledge of a Cxcl17−/− mouse, we performed an in-depth immunophenotyping analysis. Analysis of the major lymphoid compartments (LNs, spleen, bone marrow, and peritoneal cavity) revealed no significant differences between WT and Cxcl17−/− mice (data not shown). Next we focused on sites where CXCL17 is robustly expressed; specifically, we analyzed the lungs of the Cxcl17−/− mice for possible defects or alterations in the immune cell populations.

We also compared the in vitro chemotaxis activity of cells isolated from lungs of WT or Cxcl17−/− mice. Lung cells from WT mice showed robust chemotaxis responses to rmCxcl17 (Fig. 3). More than 90% of the lung cells that chemotax in response to rmCxcl17 were F4/80+ indicating that they are macrophages (data not shown). The chemotactic activity of these cells is sensitive to pertussis toxin, indicating signaling through Goi (29–33). When we tested cells from the lungs of Cxcl17−/− mice, we observed significantly reduced chemotaxis in response to Cxcl17 (Fig. 3). On the basis of this observation, we hypothesized...
that there was likely a defect in the populations of macrophages or DCs in Cxcl17−/− mouse lungs.

Like many tissues, the lung contains several subpopulations of important immune cells, including DCs and macrophages, which have been shown to be the major cell types that respond to CXCL17 by chemotaxis (4, 7, 9, 10). To investigate potential changes to these populations, we used previously reported flow cytometric approaches, which allowed us to analyze DCs, AMs, and IMs populations of the lung (34).

Analysis of the composition of macrophages and DCs of the lungs of Cxcl17−/− mice, compared with WT mice, revealed that Cxcl17−/− mice have a significant decrease in the number of AMs (Fig. 4). There is also a small decrease in DCs in Cxcl17−/− mice. We observed no changes in the population of IMs between WT and Cxcl17−/− mice. Of interest, a significant increase in a population of F4/80+ CD11cmid cells was noted (Fig. 4). Forward versus side scatter characteristics indicate that these are macrophage-like cells.

Given that CXCL17 is a chemokine, and therefore a chemoattractant, these data suggest that this new macrophage-like population of cells is dependent on CXCL17 expression within the lung to reach their final niche. The alterations in the AMs population could be due to a compensatory effect in response to increased numbers of F4/80+ CD11cmid cells.

Recent studies have demonstrated that each tissue has specific macrophage populations that can be identified by their unique gene expression profile, which includes cell surface markers, transcription factors, and transporters (35). We used this information to confirm that subpopulations of macrophages are altered in the lungs of Cxcl17−/− mice (Fig. 4). Owing to the novelty of the biomarkers specific for this population of cells, there are no Abs available to directly stain and identify them. We therefore used QRT-PCR instead to quantitate the mRNA expression of these markers in both WT and Cxcl17−/− lung samples. As shown in Fig. 5, two lung macrophage-specific markers—ATP-binding cassette, subfamily C (CFTR/MRP), member 3 (ABCC3) and nuclear receptor subfamily 1, group D, member 1 (NR1D1)—are significantly reduced in the lungs of Cxcl17−/− mice compared with WTs. Both ABCC3, a transporter, and NR1D1, a transcription factor, are highly expressed in macrophages (35–39) and are strongly expressed in cells of the monocyte lineage (DCs and macrophages) in the lung (Supplemental Fig. 2).

These data indicate that Cxcl17 is an important macrophage recruitment factor for certain populations of lung macrophages. To further explore this, we stained for CXCL17 in the human lung. As shown in Fig. 3, CXCL17 is strongly expressed in bronchial epithelium, as described (9, 11), and, importantly, it is also strongly expressed in endothelial cells of blood vessels of the lung. The latter observation strongly suggests that CXCL17 mediates recruitment of blood cells from the circulation to the lung.

Discussion

CXCL17 was the last chemokine ligand described (4) and therefore we are still making significant discoveries about its biology. We and others (4, 5, 9–11) have established that CXCL17 exhibits a predominant mucosal expression pattern. In the current study, we aimed to further investigate the function of CXCL17 in vivo.

To date, most studies involving CXCL17 have investigated roles for this mucosal chemokine in cancer (5–9). CXCL17 has been shown to promote tumor growth by acting as a proangiogenic factor.
factor (5, 9, 10) and by increasing tumor cell proliferation (6) in several types of cancer. Conversely, Hiraoka et al. (7) have shown that CXCL17, in conjunction with ICAM2, is upregulated in the precursor lesion of pancreatic cancer, in which it may play a role in immune surveillance.

Two recent studies have also investigated the connection between CXCL17 and inflammation. Lee et al. (10) have reported that CXCL17 exerts anti-inflammatory effects on LPS-activated macrophages. Lachance et al. (40) observed an increase of CXCL17 expression in a mouse model of acute cutaneous hypersensitivity. Given these findings, we wanted to establish whether inflammatory conditions are required to drive CXCL17 expression and, if so, in which mucosal tissues.

By analyzing tissues from GF, SPF, and standard (non-SPF) housed mice, we found that CXCL17 is expressed in some tissues (e.g., trachea) under homeostatic conditions but is also induced upon microbial colonization in various gut and lung tissues (Fig. 1). The expression of CXCL17 in the trachea was similar in all three groups of mice, indicating that no inflammatory stimulus is required to induce CXCL17 expression in this tissue. Conversely, CXCL17 expression is significantly elevated in tissues of the digestive tract, tongue, and lungs from mice housed under standard conditions compared with GF or SPF housed mice (Fig. 1). GF mice are not colonized by normal flora, and therefore lack the basal level of inflammation normally found in these tissues when they are colonized. In line with this, we observed that CXCL17 expression was restored when mice were housed under normal conditions that allowed them to be colonized by normal flora (Fig. 1).

Although CXCL17’s chemotactic activity has been previously analyzed (4, 6, 7, 9, 10), this property had not yet been investigated in an in vivo setting under nondisease conditions. To investigate this, we injected WT mice i.p. with recombinant Cxcl17 and analyzed the cells recruited to the peritoneal cavity after 72 h. We observed a significant increase in the number of macrophages recruited to the peritoneal cavities of these mice (Fig. 2). These results are in line with previous in vitro findings (4, 7, 9, 10). It has also been previously reported that CXCL17 will chemoattract DCs in vitro (4, 7), but we did not observe significant DC recruitment in our in vivo model (Fig. 2). This difference may be due to differences in regional DC populations. Pisabarro et al. (4) observed that PBMC-derived DCs chemotax in response to CXCL17. Given that recent studies have documented strong diversity of regional DC populations (41–43), it is likely that the DCs found in blood are different from those that would respond to i.p. injected CXCL17. Alternatively, this may reflect a difference between mouse and human CXCL17 biology.

An important tool for studying CXCL17’s biology in vivo is a Cxcl17−/− mouse. Our initial observations indicated that the Cxcl17−/− mouse is viable and fertile. Several chemokine receptor/ligand knockout mice have been generated, and some of these strains were not viable (44, 45). Given the observed viability of this mouse, we conclude that Cxcl17 does not play a significant role in development. The Cxcl17−/− mice also gained weight and otherwise exhibited normal development, indicating that CXCL17 is not likely to play a role in metabolism, unlike other mucosal chemokines like CXCL14 (21, 46).
Immunophenotyping of the Cxcl17−/− mouse revealed insights about CXCL17's in vivo activity. We chose to focus on the lung, which is a site with robust CXCL17 expression (9, 11) (Fig. 1) and a tissue for which we have previously established a role for CXCL17 in human disease because it is highly upregulated in IPF (11). Using both flow-cytometric and gene expression analyses, we observed a significant reduction in the number of macrophages present in the lungs of the Cxcl17−/− mouse compared with WT (Figs. 4, 5). These findings agree with previous studies showing that CXCL17 chemoattracts cells from the myeloid lineage (Refs. 4, 7, 9, 10 and A.M. Burkhardt, J.L. Maravillas-Montero, C.D. Carnevale, and A. Zlotnik, unpublished observations).

Given that several macrophage subpopulations exist in the lung, we investigated whether all lung macrophage populations were altered by the absence of CXCL17, or, alternatively, whether only a specific group was affected. Using cell-specific biomarkers, we identified the reduced lung macrophage population as AMs (34) (Fig. 4). We did not observe significant differences in the IM population (34) (Fig. 4). We also observed a significant increase in a population of cells that are F4/80+CD11c−/− (Fig. 4) in the Cxcl17−/− mouse. The size and complexity of these cells indicate that they are macrophage-like, and distinct from the AM and IM populations. Their possible relation to AMs remains a topic for future studies.

We conclude that CXCL17 is an important macrophage chemoattracting factor in the lungs. The decrease in the AM population is due to the absence of CXCL17 in the lungs. Chemokines are chemotactic molecules and are important for various populations of cells to home into tissues under homeostatic conditions (1–3). Conflicting data have been presented about the origin of AMs; some studies suggest that AMs originate as circulating blood monocytes that traffic into the lung (47–50), whereas other groups have generated data indicating that AMs arise from IMs (48, 51).

A recent study analyzed the transcriptome and phenotypic similarities between AMs and IMs (52). These authors showed that IMs more closely resemble the phenotype and gene expression profile of monocytes (52). Furthermore, the chemokine receptor expression profile of IMs, not AMs, more closely resembles the expression profile of monocytes (52). These studies showed that AMs and IMs differ at the transcriptional level; along with our results, these observations suggest that AMs depend on CXCL17 to home to the lung.

We should note that the CXCL17 receptor has not yet been identified; therefore, this unidentified receptor may mediate the homing of AMs into the lung. This hypothesis is also supported by our chemotaxis studies (Fig. 3) and immunohistochemical staining of human lung (Fig. 3B). The fact that CXCL17 is expressed by the endothelial cells surrounding blood vessels (Fig. 3B) strongly suggests that this chemokine is an important extravasation factor, a property shared by other members of the chemokine superfamily (53–56). CXCL17 is also strongly expressed in the bronchial epithelium, which is a site where AMs are normally located (49, 57). It is therefore possible that CXCL17 may have other functions on AMs besides allowing them (or their precursors) to home to the lung. By contrast, as mentioned above, CXCL17 has been associated with homeostatic expression of CXCL17 in the trachea (and likely bronchus). Taken together, our data suggest that CXCL17 mediates the recruitment of AMs or their precursors to the lung.

These observations also support the hypothesis that CXCL17 may play a role in the pathogenesis of IPF (11). We have reported elevated levels of CXCL17 in the bronchoalveolar lavage fluid of IPF patients (11). IPF patients are known to have an increased number of macrophages in their lungs, which could be due to the elevated CXCL17 levels.
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