Role of epithelial chemokines in the pathogenesis of airway inflammation in asthma (Review)

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Abstract. As the first barrier to the outside environment, airway epithelial cells serve a central role in the initiation and development of airway inflammation. Chemokines are the most direct and immediate cell factors for the recruitment and migration of inflammatory cells. The present review focused on the role of epithelial chemokines in the pathogenesis of airway inflammation in asthma. In addition to traditional CC family chemokines and CXC family chemokines, airway epithelial cells also express other chemokines, including thymic stromal lymphopoietin and interleukin-33. By expressing and secreting chemokines, airway epithelial cells serve a key role in orchestrating airway inflammation in asthma.

Contents

1. Introduction

Airway inflammation has been regarded as the most important pathological characteristic of asthma patients (1). Infiltration of various inflammatory cells into the airway submucosa is also the basis of airway hyper-responsiveness (AHR) and airway remodeling (2). It has been verified that the development of chronic airway inflammation in asthma is due to inappropriate airway immune responses to specific pathogens or allergens from the outside environment (3). A disrupted immune response of airway epithelial cells induces the occurrence and development of complicated airway inflammation in asthma (4,5). As they are situated between the host and the outside environment, airway epithelial cells are the physical defense line against microorganisms, gases and allergens. In recent years, the structural and functional homeostasis of airway epithelial cells in asthma pathogenesis has attracted increasing attention (5,6). Airway epithelial cells rapidly identify and respond to microbes, tissue damage or cellular stress via expression of pattern recognition receptors (PRRs). Epithelial PRR activation then leads to the release of cytokines, chemokines and antimicrobial peptides, which further attract and activate innate and adaptive immune cells (7,8). Notably, an increasing number of studies have confirmed that multiple pro-inflammatory mediators (including cytokines and chemokines) serve a major role in the recruitment and invasion of airway inflammatory cells (7,9,10).

Chemokines are the most direct and immediate cell factors that selectively induce the migration of specific inflammatory cells by binding with different receptors (11). They are a group of low molecular weight (mostly 8-10 KDa) polypeptides that are designated for their targeted cell chemotaxis. There are four conserved cysteines in the protein structure of chemokine molecules. Chemokines are divided into the following four families (CC, CXC, C and CX3C) based on where other amino acids are inserted between the first two cysteines near the N-terminus (12). By interacting with corresponding receptors, chemokines strongly contribute to the chemotaxis of neutrophils, eosinophils, basophils, monocytes, mast cells, dendritic cells (DCs), natural killer (NK) cells, T lymphocytes and B lymphocytes. There is not a simple one-to-one correspondence between chemokines and chemokine receptors. One chemokine receptor can be activated by different chemokines and one chemokine can bind to different chemokine receptors (13). The CC family contains ~28 types of chemokines with strong chemotaxis effects on almost all inflammatory cells (except neutrophils). The CXC chemokine family contains more than 15 types of chemokines, which possess potent effects on the recruitment of neutrophils and monocytes. Besides these four traditional cytokine families, there is a growing

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number of cytokines showing strong chemotactic effects which are also classified as chemokines (14,15). Studies have shown that a variety of cells are involved in expression and secretion of chemokines, including macrophages, monocytes, eosinophils, basophils, neutrophils, mast cells, DCs and lymphocytes (10,11,13). The participation of a variety of effector cells leads to the cascade of events triggering the activation of diverse immune responses. It has been identified that airway epithelial cells act as the key orchestrator to airway inflammation in asthma (16). Airway epithelial cells selectively produce a number of different chemokines that can induce various types of inflammatory cells which would release a variety of inflammatory factors. Such inflammatory factors cause the immediate phase reaction of airway inflammation mediated by immunoglobin (IgE) and induce chronic persistence airway inflammation with eosinophils and T helper cell (Th)2 lymphocytes (9,17). The present review focused on the expression and biological characteristics of chemokines in airway epithelial cells and the role of these epithelial chemokines in the pathogenesis of airway inflammation in asthma (Table I).

2. Expression properties of epithelial chemokines

For airway epithelial cells, the expression of chemokines is regulated at several levels. Different expression properties of chemokines from diverse research models all indicate the importance of chemokines during the pathogenesis of airway inflammation in asthma (18).

Expression properties of CC family chemokines in airway epithelium. The early immune response is mediated mainly by inflammatory cytokines interleukin (IL)-1 and tumor necrosis factor-α (TNF-α). It has been reported that IL-1β and TNF-α are present in the epithelial environment within hours of infection (19,20). IL-1β and TNF-α then induce the expression of chemokines in epithelial cells (11). It has previously been demonstrated that TNF-α stimulates the expression of C-C motif chemokine ligands CCL2, CCL4, CCL5, CCL11 and CCL20. Furthermore, airway epithelial cells release CCL5 and CCL20 upon stimulation by IL-1β (18). IL-1β can also induce the expression of CCL3 and CCL4 in airway epithelial cells by activating nuclear factor (NF)-κB. In addition, NF-κB also activates transcription of the gene encoding CCL2 as its promoter contains an NF-κB binding site (21,22).

Several other inflammatory cytokines can induce the expression of certain chemokines. Previous studies have revealed that TNF-α in combination with IL-4 or IL-13 upregulates the expression and secretion of CCL17 in epithelial cells (23,24). It has also been indicated that CCL11 and CCL20 are produced following IL-4 or IL-13 stimulation (25). Furthermore, it has been demonstrated that clusterin induces the production of CCL20 by regulating the oxidative stress environment in airway epithelial cells from mice studies (26). Previous studies have demonstrated that microRNA-34a, 15-lipoxygenase and histamine are important regulators for CCL22 in airway epithelial cells (27-29).

In addition, airway epithelial cells produce chemokines in response to immunological environmental factors including microbial and viral stimuli (11). Viral or bacterial infection induces the secretion of high levels of CCL2, CCL5 and CCL20 by airway epithelial cells (30). Furthermore, infection by viruses increases CCL5 expression in different types of cells. For example, respiratory syncytial virus infection results in enhanced expression of CCL5 in human nasal mucosa and gland epithelial cells, and infection by influenza virus induces CCL5 expression in human bronchial tissues and nasal polyp epithelial cells (31). In addition, Der p allergens from house dust mites induce CCL17 expression in bronchial epithelial cells which appears to be mediated by a disintegrin and metalloproteinase-dependent phosphorylation of epidermal growth factor receptor and subsequent activation of mitogen-activated protein kinase (MAPK) and NF-κB (32).

Expression properties of CXC family chemokines in airway epithelium. It has been demonstrated that IL-17 promotes the expression of CXCL1 and CXCL5 in bronchial epithelial cells and that IL-17 potentially promotes CXCL1 expression mainly through the extracellular regulated protein kinases (ERK) or MAPK pathway (33). At the same time, different cytokines stimulate CXCL8 secretion under the control of different signaling pathways, including NF-κB, ERK, c-Jun N-terminal kinase (JNK) and MAPK pathways (34). Additionally, Janus kinase (JAK) and the synergistic effect of TNF-α and interferon-γ can induce CXCL10 expression in airway epithelial cells (35). On this basis, these associated signaling molecules have also been used as potential targets of anti-inflammatory treatment. It has been identified that the inhibition of JAK pathway in the airway epithelium may provide an alternative anti-inflammatory approach to glucocorticosteroid-resistant diseases *in vitro* (36). It has also been observed that the long-acting β2 agonists downregulate poly I:C-induced CXCL10 expression in bronchial epithelial cells via the β2 adrenoreceptor-cyclic adenosine monophosphate and JNK pathways *in vitro* (37).

Expression properties of other chemokines in airway epithelium. Various cytokines including thymic stromal lymphopoietin (TSLP) and IL-33 secreted by airway epithelial cells have previously been identified to possess very strong recruitment effects on inflammatory cells. They are also classified as chemokines not belonging to the traditional four classic chemokine families (38,39).

Previous studies have revealed that TNF-α and IL-1β can induce the expression of IL-33 (40). Park *et al* (41) verified that TNF-α stimulates IL-33 expression in primary nasal epithelial cells and A549 cells via the NF-κB, ERK and MAPK pathways *in vitro*. Furthermore, IL-33 has been reported to induce the production of TSLP in bronchial epithelial cells following activation by antigens (42). Respiratory syncytial virus infection can also rapidly transfer stress signals through the JNK and MAPK pathways via direct stimulation of epithelial cells to upregulate expression of TSLP (43).

3. Functional properties of chemokines and associations between chemokines and asthma

Effect of chemokines on DCs and T cells. Recruitment of Th2 cells and the subsequent production of Th2-type cytokines form the main characteristics of asthma airway inflammation (44).

Table I. Airway epithelium chemokine expression associated with asthma (8,9,13).

System name	Generic name	Full name	Receptor	Cell types affected
CC family				
CCL2	MCP-1	Monocyte chemotactic protein-1	CCR2, 10	Monocyte, T lymphocyte, basophil, NK cell
CCL3	MIP-1α	Macrophage inflammatory protein-1α	CCR1, 3, 5	Macrophage, eosinophil, T lymphocyte, DCs, neutrophil, NK cell
CCL4	MIP-1β	Macrophage inflammatory protein-1β	CCR5,8	Lymphocyte, monocyte
CCL5	RANTES	Regulated upon activation normal T-cell expressed and secreted	CCR1, 3, 5	Eosinophil, monocyte, memory T cell, $CD4^{+}$T cell, basophil
CCL11	Eotaxin-1	Eotaxin-1	CCR3, 5	Eosinophil
CCL13	MCP-4	Monocyte chemotactic protein-4	CCR2, 3	T lymphocyte, eosinophil, basophil, monocyte
CCL17	TARC	Thymus activation regulated chemokine	CCR4	Th2 cell
CCL20	MIP-3α	Macrophage inflammatory protein-3α	CCR6	iDCs, T lymphocyte, B lymphocyte
CCL22	MDC	Macrophage-derived chemokine	CCR4	Th2 cell, DCs, NK cells
CXC family				
CXCL1	GRO-α	Growth-regulated oncogene-α	CXCR1, 2	Neutrophil
CXCL5	ENA-78	Epithelial-derived neutrophil-activating peptide 78	CXCR2	Neutrophil
CXCL8	IL-8	Interleukin-8	CXCR1, 2	Neutrophil, eosinophil, T lymphocyte, NK cell
CXCL10	IP-10	Interferon-inducible protein-10	CXCR3, 4	Eosinophil, neutrophil, monocyte, T lymphocyte
Non CC or CXC family				
TSLP	No	Thymic stromal lymphopoietin	TSLPR	DCs, Th0 cell, Th2 cell
IL-33	No	Interleukin-33	IL-33R, ST2	DCs, Th2 cell, ILC2s

DCs, dendritic cells; NK, natural killer; iDCs, immature DCs; ILCs, innate lymphoid cells.

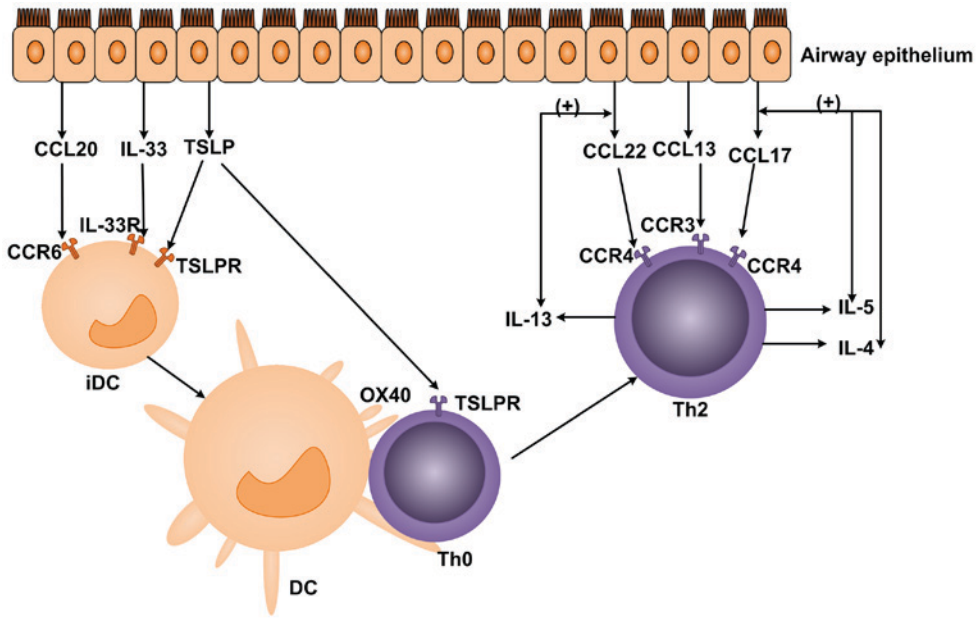

Figure 1. The effect of chemokines on DCs and T cells. CCL20, IL-33 and TSLP secreted by airway epithelial cells combine with CCR6, IL-33R and TSLPR on iDCs to serve a role in chemotaxis. CCL13, CCL17 and CCL22 combine with CCR3 and CCR4 on Th2 cells to induce chemotaxis. DCs, dendritic cells; CCL, C-C motif chemokine ligand; IL, interleukin; TSLP, thymic stromal lymphopoietin; CCR, C-C chemokine receptor; IL-33R, IL-33 receptor; TSLPR, TSLP receptor.

DCs are sentinels of the adaptive immune system as they can induce the differentiation of Th2 cells. The key role of DCs in asthma pathogenesis has been a subject of attention for more than 15 years (1).

In the pathogenesis of asthma, the secretion of CCL20, IL-33 and TSLP is substantially increased following stress by allergens and other pathogenic substances. C-C chemokine receptor CCR6, IL-33R and TSLPR (corresponding receptors for CCL20, IL-33 and TSLP respectively) are expressed on immature DCs (iDCs). By binding with these receptors, CCL20, IL-33 and TSLP activate iDCs and promote their maturation (26,42). DCs then migrate to the T cell zone in mediastinal lymph nodes, where they activate T cells via antigen presentation and co-stimulation. Furthermore, TSLP upregulates the expression of surface co-stimulatory molecules, including CD40, CD80 and CD86 on DCs. Under the influence of secreted cytokines and membrane-expressed molecules including OX40 L, Jagged1, IL-6 and leukotrienes C4, activated inflammatory DCs interact with naive $CD4^+$T cells and induce the differentiation of Th2, Th17 and follicular helper T cells (45,46). CCR3 and CCR4 surface receptors of Th2 cells directly bind to chemokines secreted by epithelial cells. CCR4 interacts with CCL17/CCL22, and CCR3 interacts with CCL13 (27). Animal studies have indicated that targeted blocking of CCR4/CCR3 receptors can significantly reduce the eosinophil ratio in the bronchoalveolar lavage fluid of asthmatic model mice (47). Following prompting by the actions of these chemokines, Th2 cells infiltrate into the site of inflammation where they secrete cytokines including IL-4, IL-5, IL-13 and TNF-α (Fig. 1). These cytokines in turn cause enhanced airway mucus secretion and airway epithelial structure destruction, further provoking airway inflammation and AHR (48,49). IL-4 induces B cell activation and the secretion of IgE; IL-13 causes goblet cell metaplasia, AHR and increases the expression of adhesion molecules on vascular endothelial cells (44,50). Furthermore, IL-4 and IL-13 can also promote the secretion of CCL17 by airway epithelial cells, and IL-13 can promote the secretion of CCL22 (23). These chemokines, which result from cascade amplification, further induce the aggregation of Th2 cell infiltration. The specific enhanced expression of TSLP in airway epithelial cells results in initial $CD4^+$T lymphocyte proliferation and Th2 cell differentiation (38). Conversely, targeting TSLP with short hairpin RNA or antibodies, alleviates airway inflammation and decreases epithelial CCL17 in a murine model of asthma (51,52).

Effect of chemokines on eosinophils, neutrophils and innate lymphoid cells (ILC)2. In addition to activated DCs and Th2 cells, eosinophils also act as key effector cells in the airway inflammation of asthma. The invasion of eosinophils in the airway is closely associated with the severity of asthma (53). Eosinophils initially form in the bone marrow and differentiate from progenitor cells. By rolling adhesion and exudation, eosinophils interact with endothelial cells. Eosinophils are activated to release granule-associated proteins, which cause airway epithelial injury, smooth muscle contraction, inflammatory cell infiltration and AHR (54). In this process, CCL5 and CCL11 function as potent eosinophil chemoattractants by binding to CCR3 (Fig. 2). CCL11 also induces eosinophil chemotaxis via the activation of ERK and MAPK pathways (55). CXCL8 and CXCL10 can also bind to CXCR2 and CXCR3, respectively, on eosinophils to induce the recruitment of eosinophils. Following the recruitment to the airway inflammation area, eosinophils release various inflammatory mediators and toxic proteins (including eosinophil cationic protein, myelin basic protein, palmitic acid and IL-5 which further aggravate airway inflammation. Eosinophils also produce protein particles to cause tissue damage (56) and respiratory burst (57,58).

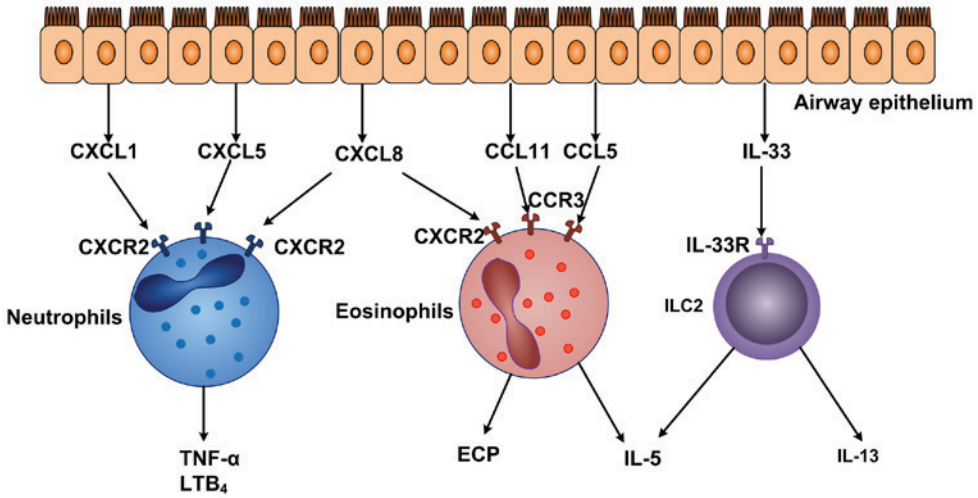

Figure 2. The effect of chemokines on eosinophils, neutrophils and ILC2. CXCL1, CXCL5 and CXCL8 secreted by airway epithelial cells combine with CXCR2 on neutrophils to serve a role in chemotaxis. CCL5, CCL11 and CXCL8 combine with CCR3 and CXCR2 on eosinophils to induce chemotaxis. IL-33 combine with IL-33R on ILC2 to induce the activation of ILC2. ILC, innate lymphoid cell; R, receptor; CCR, C-C chemokine receptor; IL, interleukin.

Although asthma is classically associated with eosinophilia and Th2 cytokines, certain asthma patients exhibit a neutrophil-predominant phenotype without evident Th2 cytokines. CXCL8 and CXCL10 possess a strong chemotactic effect on neutrophils (Fig. 2). Takaku *et al* (58) identified that CXCL10 and CXCL8 are elevated in asthma phenotypes with increasing eosinophils and neutrophils in airways. In addition, CXCL8, CXCL1 and CXCL5 can bind to CXCR2 (a specific surface receptor on neutrophils), which can activate neutrophils and attract them to inflammation sites. These chemokines also promote expression of adhesion molecules, (including CD11a, -b, -c and CD18) and cause cell deformation, eosinophil degranulation and respiratory burst (59-61). In addition, TNF-α, leukotriene B4 and other inflammatory mediators produced by activated neutrophils further exacerbate airway inflammation, leading to airway submucosal edema and goblet cell metaplasia (62).

An increasing number of studies have demonstrated that ILC2 s contribute to the initiation and maintenance of the adaptive Th2 immune response (63,64). By binding to IL-33R on ILC2 cells, IL-33 promotes production of IL-5 and IL-13 by ILC2 (Fig. 2). IL-13 secreted by ILC2 cells can bind to IL-13R on macrophages, which further induce the activation of macrophages (65). In addition, early eosinophilia in the lung is driven by IL-5 that also supports the development of eosinophils in the bone marrow. Consequently, ILC2 cells contribute to Th2 cell-mediated lung inflammation in the pathogenesis of asthma (66).

Effect of chemokines on monocytes. Monocytes express specific high-affinity receptors for CCL2, CXCL10, CCR2 and CXCR3 (9). Macrophage recruitment occurs via a chemotactic gradient of monocyte selective chemokines. Following activation and recruitment, monocytes release superoxide anions and lysozymes (67). At the same time, surface-specific adhesion molecules CD11c and CD11b are expressed on monocytes, which are involved in the regulation of airway inflammation. In addition, the increased expression of integrin β2 and α4 is accompanied by upregulated IL-1 and IL-6 (68). Interactions between mucosal epithelial cells and macrophages are pivotal to allergic lung inflammation. Increased expression of CCL2 has been reported in asthmatic airway epithelial cells, blocking the CCL2-CCR2 axis and attenuating the asthma phenotype in other animal models of asthma (69).

4. Conclusion

The airway immune response is mediated by airway epithelial cells through the secretion of chemokines. First, chemokines selectively induce various inflammatory cells to accumulate directly at the site of inflammation. Chemokines further induce stromal and inflammatory cells and produce more chemokines, resulting in a cascade effect that results in more severe tissue damage indirectly. The present review provides novel considerations for asthma airway inflammation research from a chemokine perspective, and a fresh approach to the clinical therapy of asthma.

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Availability of data and materials

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Authors' contributions

ChL and XQ conceived and designed this review. XZ, YX, XQ and HL collected the relevant papers. CL, MT and JJ obtained and analyzed the relevant data from the references. ChL wrote the review.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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