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Chemokines in allergic airway disease

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Abstract

Expression of chemokine receptors on T helper 2 cells and eosinophils has been postulated to be the mechanism by which these cells are selectively recruited to the lung during allergic inflammatory reactions. Mouse models have provided evidence to show that blocking the ligands for these receptors is successful in abrogating the pathophysiological effects of allergen challenge. However, recent studies describing the effect of genetic deletions of these chemokine receptors have not confirmed the results obtained with ligand knockouts or neutralising antibodies. Coupled with the realisation that, because of a lack of species cross-reactivity, it is not possible to test small molecule antagonists against human receptors in the original *in vivo* animal models, the future of chemokine receptor therapeutics is in question. However, recent advances have been made regarding the therapeutic potential of blocking the chemokine receptors CCR3, CCR4 and CCR8 in allergic airway disease.

Introduction

Allergic inflammation, such as asthma, is a T helper (Th)2-driven response associated with the selective recruitment of allergen-specific Th2 cells to sites of inflammation. These Th2 cells influence the inflammatory response through generation of specific cytokines, including interleukin (IL)-4, IL-13 and IL-5. One important consequence of Th2 cell involvement is the associated influx of large numbers of eosinophils, which are thought to contribute to the pathogenesis of the disease. Allergic inflammation in the lung is characterised by airway hyperresponsiveness (AHR). Eosinophils, Th2 cells and mast cells can all contribute to AHR, although controversy remains over which cell type is the predominant effector of this response. In developing therapies for asthma, the goal is to inhibit AHR and not just leukocyte recruitment.

Chemokines are a group of structurally related chemotactic cytokines that signal through 7-transmembrane G-protein-coupled receptors expressed by leukocytes. The discovery that certain chemokine receptors are differentially expressed on the surface of effector T cells has suggested that this might be the mechanism by which Th2 cells are selectively recruited to the lung. *In vitro* analysis has determined that not only do effector T cells express a restricted repertoire of receptors but also that they preferentially migrate to the chemokines that bind these receptors [1,2]. Thus, it has been shown that CCL11 (eotaxin), CCL22 (monocyte-derived chemokine), CCL17 (thymus and activation-regulated chemokine) and CCL1 (I-309 [human] or TCA-3 [mouse]) are chemokines which induce the selective migration of Th2 cells but not Th1 cells. CCL11 binds exclusively to the chemokine receptor (CCR)3, whereas CCL22 and CCL17 both interact with CCR4. CCL1 is the only known ligand for CCR8. Interestingly, CCR3 is also expressed by eosinophils, for which

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CCL11 is a potent chemoattractant. The only other chemokine receptor expressed by eosinophils is CCR1, but this is generally expressed at very low levels. Interest in CCR3, CCR4 and CCR8 as potential therapeutic targets in asthma developed when it was discovered that these receptors exhibited restricted expression profiles on cells believed to be involved in the asthmatic response. CCR3 is reported to be expressed by eosinophils, Th2 cells, mast cells and basophils, whereas CCR4 and CCR8 are expressed by Th2 cells (Figure 1). Thus, these chemokine receptors are potential targets for the treatment of allergic inflammation, as they have the advantage of being expressed by selective leukocyte populations.

In this review, we describe recent findings from *in vivo* studies of allergic inflammation regarding the function of chemokines and their receptors. These studies include those using both ligand blockade and receptor knockout (KO) strategies. We discuss how recent advances in the fields of chemokine biology and allergic airway inflammation allow us to better interpret some of the conflicting results. Finally we consider how the results of all of these studies impact on the search to find chemokine receptor antagonists for anti-asthma therapeutics.

CCL11 and CCR3

Multiple studies have shown that neutralisation of CCL11 results in a decrease in both airway inflammation and AHR [3–5]. More specifically, it has been shown that CCL11 blockade reduces trafficking of Th2 cells and eosinophils [6]. In contrast, the CCL11 KO mouse showed only partial protection against development of allergic airway inflammation, reinforcing the idea that there is a certain amount of redundancy in the chemokine network [7,8]. Three members of the CCL11 family have been identified in humans (CCL11, CCL24 [eotaxin-2] and CCL26 [eotaxin-3]) [9–11], whereas only two forms are expressed in the mouse [12,13]. These eotaxins could have distinct, as well as overlapping, functions. Although they are all upregulated during allergen challenge [14,15], recent studies have determined that, in response to the Th2 cytokine IL-4, they are generated by distinct cell types [16,17]. These findings suggest that CCL11, CCL24 and CCL26 may be regulated both temporally and spatially during disease progression.

Antagonism of the CCL11 receptor (CCR3) was predicted to be a valid therapeutic strategy for the treatment of asthma. However, the recent development of a CCR3 KO mouse has added further complexity to our understanding of how CCR3 regulates leukocyte trafficking to the lung during allergic inflammation [18••]. Although eosinophil recruitment to the lung after allergen challenge was significantly reduced in CCR3 KO mice, AHR was unexpectedly increased [18••]. It was proposed that this was a result of increased accumulation of mast cells in the trachea following allergen challenge. Related studies showed that CCR3-deficient mice were completely protected from allergen-induced AHR when the model system was changed so that mast cells were not recruited to the trachea [19••]. These studies indicate that, in addition to Th2 cells and eosinophils, mast cells may also be critical for the development of AHR.

CCL22, CCL17 and CCR4

Neutralising either CCL22 or CCL17 has been shown to abrogate lung eosinophilia and AHR [20,21]. It was proposed that this was caused by inhibition of Th2 cell trafficking. Further studies utilised a model based on the adoptive transfer of allergen-specific effector T cells to track Th2 cell migration to the lung following allergen challenge in mice receiving anti-CCL22 antibodies [6]. These experiments established that CCL22 and CCR4 contribute to the recruitment of Th2 cells to the lung, demonstrating for the first time an *in vivo* relevance for the expression of this receptor on T cells. In contrast, CCR4 deficiency

afforded no protection against the development of allergic inflammation or AHR [22]. This might be explained by the intrinsic differences either in blocking a ligand rather than a receptor, or in using a genetically deficient mouse rather than neutralising antibodies. As antibodies against CCR4 are not available, this theory cannot be tested directly. An alternative explanation for these results is that there are other, as yet undiscovered, receptors for CCL22 and CCL17. In a separate study, the effect of CCR4 KO was examined in a model of chronic allergic airways disease; a significant reduction in both eosinophilia and AHR was reported [23•]. A potential caveat of these findings is that the allergen used was *Aspergillus fumigatus*, and it was noted that fungal spores were more rapidly cleared in the CCR4-deficient mice. Thus, it is not known whether the observed reduction in allergic inflammatory response was a direct effect, caused by a reduction in Th2 cell trafficking, or an indirect effect, caused by enhanced elimination of the fungal spores by a distinct CCR4-dependent mechanism. Indeed, protection from lipopolysaccharide-induced lung inflammation was initially reported in CCR4-deficient mice [22]. Taken together, these studies indicate that CCR4 might be important in modulating both the innate and acquired immune responses.

CCL1 and CCR8

The *in vivo* role of the CCL1/CCR8 chemokine axis in Th2-mediated inflammation is more controversial. Recent studies have shown that, although both CCL1 protein and CCR8 mRNA are upregulated in the murine lung following allergen sensitisation and challenge, neutralisation of the ligand has no effect on recruitment of Th2 cells to the lungs [24••,25••]. Interestingly, one of these studies reported no effect of CCL1 blockade on eosinophil recruitment [25••], whereas the other reported a modest reduction in eosinophil recruitment [24••]. Moreover, in the latter study, it was shown that direct instillation of CCL1 into the lungs of allergen-sensitised challenged mice induced the recruitment of eosinophils but not Th2 cells. Taken together, these data indicate that CCL1 is unlikely to be involved in recruitment of Th2 cells to the lung after allergen challenge, but could possibly play a role in eosinophil trafficking. Interestingly, both studies failed to show an effect on AHR.

Intriguingly, three CCR8 KO studies have been reported that give very different insights into the functional role of CCR8 in allergic reactions *in vivo*. The first study demonstrated that CCR8 KO mice had diminished Th2 responses and impaired eosinophil recruitment in a variety of Th2-driven airway inflammation models [26••]. In contrast, the two other studies found no effect of CCR8 deficiency on the development of allergen-driven airway inflammation [25••,27••]. A CCR8 blocking antibody was also used, but did not affect development of inflammation [27••]. Differences in either the model protocol or the genetic background of the CCR8KO mice might explain the variation seen in the pathology of these mice. These data, taken together with findings from the CCL1 blocking studies, imply that the CCL1/CCR8 axis might be involved in recruitment of eosinophils in some models. However, it seems unlikely that CCR8 is important for specific recruitment of Th2 cells to the lung *in vivo*.

CXCL12 and CXCR4

CXCR4 is expressed constitutively on all T cells and on a wide range of other cells, including $CD34^+$ stem cells, B cells and monocytes. It is not, however, expressed by eosinophils. As deficiency of either CXCR4 or CXCL12 (SDF-1α) is lethal, it was originally hypothesised that CXCR4 played an important role in the homeostatic homing mechanism of multiple leukocyte populations. Therefore, it was surprising that blockade of this chemokine receptor with a blocking monoclonal antibody caused a significant reduction in both airway inflammation and AHR [28]. These results were interpreted as evidence that

CXCR4 plays a role in Th2 cell trafficking during allergic inflammation. Interestingly, although CXCR4 is an unlikely therapeutic target because of its widespread expression, a recent paper by Lukacs, Berlin, Schols, Skerlj and Bridger [29•] showed that CXCR4 blockade with the specific CXCR4 antagonist AMD3100 effectively abrogates both leukocyte recruitment and AHR in a murine model of allergic inflammation. This therefore represents the first publication showing that a small molecular weight antagonist directed against a specific chemokine receptor can modify disease progression.

Chemokine receptor expression after allergen challenge of atopic asthmatics

To establish a role for specific chemokines and their receptors in allergic airway inflammation in humans, several studies have examined chemokine receptor expression on T cells within the lungs of asthmatic patients following allergen challenge. In one such study, significantly greater numbers of $CCR4^+$ T cells were found in bronchial biopsies after segmental allergen challenge than in pre-challenge biopsies, biopsies from non-atopic patients or biopsies from patients with 'Th1-type' lung diseases such as sarcoidosis or chronic obstructive pulmonary disease [30••]. Over 90% of T cells were $CCR4^+$ in allergen-challenged atopic asthmatics; the authors concluded that these were probably Th2 cells, as they co-stained for IL-4. 28% of these $CCR4^+$ T cells were also found to be $CCR8^+$. Surprisingly, in this study, the authors were unable to detect any T cells expressing CCR3 in the airways, with expression being confined to eosinophils. Expression of CCL22 and CCL17 was increased in airway epithelium following segmental allergen challenge. Interestingly, although expression of CCL1 was not detected, the number of $CCR8^+$ cells infiltrating the airway mucosa was found to correlate with the degree of airflow limitation during the late-phase reaction. Another study has also found that allergen challenge promotes recruitment of $CCR4^+$ T cells to either the lung or skin after allergen challenge of atopic asthmatics [31]. Together, these data support the idea that Th2 lymphocytes are recruited to the airways by interaction both of CCL22/CCL17 with CCR4 and, perhaps, CCL1 with CCR8.

Chemokine receptor expression is dynamic *in vivo*

There are various aspects of chemokine receptor biology that influence the conclusions drawn from individual studies *in vitro* and *in vivo*. The reported selectivity of chemokine receptor expression is appealing in terms of anti-inflammatory therapy, as it is possible to target selected leukocyte populations. However, our current knowledge of chemokine receptor expression has been gained largely from studies of isolated blood leukocytes and, in the case of T cells, on artificially polarised T cell lines or clones. There is now evidence from both *in vitro* and *in vivo* studies to show that chemokine receptor expression can be modulated either temporally or by the local tissue environment. Certainly, chemokine expression on T cells can be altered after activation, as well as during differentiation [32,33]. Eosinophils in bronchoalveolar lavage fluid from patients with eosinophilic lung disease express low levels of CCR3 and increased levels of CXCR4 compared with blood eosinophils, implying that eosinophils in different tissue compartments express a different receptor repertoire [34]. Moreover, injection of either CCL11 or CCL24 into atopic or non-atopic skin induces recruitment of neutrophils, as well as eosinophils and basophils [35•]. Although the authors found low levels of CCR3 on blood neutrophils, eotaxin did not elicit migration of neutrophils *in vitro*. Similarly, *in vivo* delivery of CCL1 to allergen-sensitised mice resulted in recruitment of eosinophils rather than Th2 cells [24••]. This effect of CCL1 on eosinophil recruitment might relate to the recent observation that allergen-sensitised eosinophils exhibit an altered repertoire of chemokine receptors [36]. Thus, in contrast to eosinophils isolated from the blood of wild-type mice or IL-5 transgenic mice, eosinophils

from the bronchoalveolar lavage fluid of allergen-sensitised mice express CCR8 and migrate to CCL1. All of these studies imply that cell surface expression of chemokine receptors is a dynamic process *in vivo*, which might not necessarily be mimicked by experiments on isolated cells *in vitro*.

Relevance of mouse models to human disease

A comparison of the methodologies used in the animal studies cited in this review reveals some important differences. Protocols differ with respect to the allergen used, the mode of sensitisation and the number and timings of airway challenges. These differences are sometimes reflected by changes in the extent and duration of inflammation (compare [24••] with [25••]) [37], but can also result in mechanistic differences in the development of the disease (e.g. compare [18••] with [19••]) (Table 1). Therefore, results of individual studies should be interpreted with this in mind. Differences between model protocols might also contribute to the inconsistencies in data obtained by various groups. In addition, human asthma is a chronic inflammatory condition, whereas mouse models of asthma are generally acute and short-term. It could be argued, therefore, that models with evidence of chronic inflammation might better reflect human disease, and are more relevant when trying to determine the therapeutic potential of drugs for the treatment of asthma in humans.

Prospects for therapeutic intervention

Animal data for blocking chemokines are compelling, and the prospect of targeting chemokine receptors on leukocytes is attractive because G-protein-coupled receptors are historically good targets. However, the perception that CCR3, CCR4 and CCR8 play a critical role in the selective recruitment of Th2 cells to sites of allergic inflammation has not been confirmed by *in vivo* studies with chemokine receptor KO mice. Further studies are necessary to determine whether these results are caused by the model system studied (i.e. the use of KOs versus antibodies) or the particular allergen used. When trying to understand and manipulate recruitment of Th2 cells to tissue sites, further complexity arises from the realisation that T regulatory cells, which can attenuate the allergic response, express a similar chemokine receptor repertoire to Th2 cells. Thus, $CD4^+/CD25^+$ regulatory T cells isolated from blood express CCR4 and CCR8, and differentially migrate to their ligands [38]. Future work will be necessary to determine whether regulatory T cells from lungs express similar patterns of receptors, and whether it is possible to influence recruitment of allergen-specific Th2 cells by promoting the development and movement to the lung of regulatory T cells.

Another challenge facing the pharmaceutical industry is to develop small molecule inhibitors of chemokines, given that species cross-reactivity for most chemokine receptors is lost as the affinity for the human receptor increases [39,40••]. Thus, *in vivo* validation in animal models as ‘proof-of-concept’ is impossible, as has been the case for BX471, a small molecule antagonist of CCR1 [41]. When looking for chemokine receptor antagonists for asthma, it is possible (although expensive) to use large animals, as there are allergy models using non-human primates. However, despite these potential problems, the number of small molecule receptor antagonists is growing rapidly, and programmes for CXCR2, CXCR4, CCR1 and CCR5 have entered Phase I clinical trials [40••,42].

Conclusions

Mouse models have generated vast amounts of data regarding the role of specific chemokines in recruiting leukocytes to the lung after allergen challenge. However, the validity of these data depends on the ability of the model to represent the human disease. Further work is needed to determine how CCR3, CCR4 and CCR8 interact to mediate the

recruitment of Th2 cells and eosinophils to the allergic lung, and to confirm these results in human studies. Although some studies appear contradictory, further analyses of the methods employed and the wider use of reagents in several models are likely to answer these apparent contradictions. With small molecule antagonists for several chemokine receptors now in development, it seems likely that a new generation of therapeutics for asthma will ultimately be available.

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Abbreviations

AHR	airway hyperresponsiveness
CCR/CXCR	chemokine receptor
IL	interleukin
KO	knockout
Th	T helper

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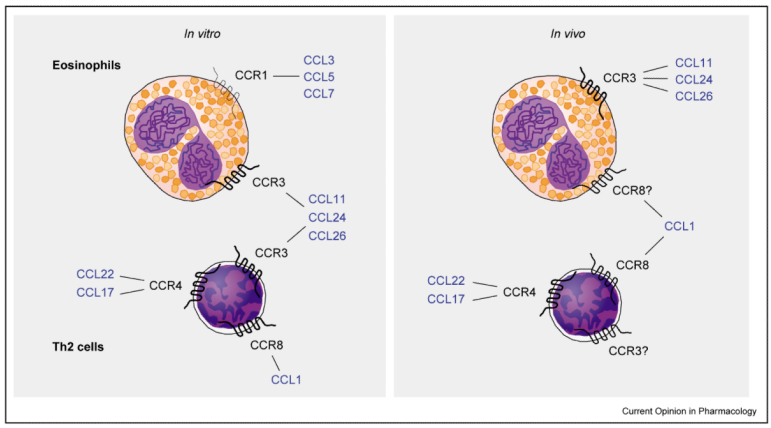

Figure 1.
Potential chemokine receptor–ligand interactions on human eosinophils and Th2 cells. Recent studies have highlighted differences between *in vivo* and *in vitro* receptor expression.

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Table 1

Contrasting effects of blocking chemokine receptors or their ligands during allergic airway inflammation.

Receptor	Knockout	Ligand	Blocking antibodies
CCR3	Decreased eosinophils, increased AHR [18••]	CCL11	Decreased eosinophils [4,7,8]
			Reduced Th2 recruitment [6]
CCR4	No protection [22]	CCL22	Decreased eosinophils and AHR [20]
	Reduced AHR [23•]	CCL17	Reduced Th2 recruitment [6]
			Decreased eosinophils and AHR [21]
CCR8	Decreased eosinophils [25••]	CCL1	Decreased eosinophils [24••]
	No protection [24••,26••]		No effect [24••]