

Immunological mechanisms behind the cystic fibrosis-ABPA link

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Allergic bronchopulmonary aspergillosis (ABPA), a pulmonary hypersensitivity disease mediated by an allergic response to *Aspergillus fumigatus* (*A. fumigatus*), occurs preferentially in disease conditions with an impaired pulmonary immunity, especially in cystic fibrosis (CF) and allergic asthma. The pathophysiological mechanisms underlying the link between CF and ABPA are poorly understood. Animal and human data support a critical role for chemokines, especially CCL17 and its receptor CCR4, in ABPA. A summary and discussion of the immunological mechanism involved in the pathogenesis of ABPA with a focus on CF lung disease and the role of chemokines is presented here.

Keywords Allergic bronchopulmonary aspergillosis (ABPA), *aspergillus*, cystic fibrosis (CF), chemokines, chemokine receptors, Th2, TARC, CCL17, CCL22, CCR4

Allergic bronchopulmonary aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA), a pulmonary hypersensitivity disease mediated by an allergic response to *Aspergillus fumigatus*, occurs preferentially in disease conditions with an impaired pulmonary immunity, especially in cystic fibrosis (CF) and allergic asthma [1]. *A. fumigatus* colonization occurs in up to 60% of CF patients [2], but ABPA is diagnosed in only about 5–15% of CF patients depending on region, patient cohorts and diagnostic criteria [3–6]. However, when ABPA occurs in CF patients it can have detrimental consequences and frequently leads to acute worsening of the respiratory status. Without early diagnosis and specific treatment, ABPA can progress to a chronic state and may lead to bronchiectasis and severe lung fibrosis [1,5]. The diagnosis of ABPA is traditionally based on the criteria according to Nelson [2], including wheezing, new

pulmonary infiltrates, elevated total IgE serum levels, elevated specific IgE and IgG serum levels against *A. fumigatus*, positive skin prick test reactivity against *A. fumigatus* and the detection of *A. fumigatus* in sputum.

Despite these criteria, the diagnosis of ABPA in CF patients remains difficult since some of the major criteria are seen regularly in CF patients without ABPA [7,8]. Especially in CF patients with recurrent ABPA episodes, the differentiation between an exacerbation due to ABPA or due to other pulmonary infections is difficult. Furthermore, ABPA shares characteristics with atopy, present in about 25% of CF patients [9]. Total serum IgE levels are commonly used for the diagnosis and the monitoring of ABPA episodes in CF patients [10]. However, total IgE serum levels vary markedly with age and atopic background [11] and a proportion of ABPA patients has been reported to have low total serum IgE levels [8,10,12]. IgE isotype switching was recently described to be accomplished primarily at the pulmonary site in patients with allergic asthma, which might explain the absence of increased serum IgE in a subset of ABPA patients [13]. There is a need for a more profound understanding of the immunological link between CF and ABPA in order to develop ABPA-specific biomarkers and effective therapeutical approaches.

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Allergic bronchopulmonary aspergillosis as a Th2 disease

Several lines of evidence suggest ABPA as a Th2-driven disease [3,6]. *A. fumigatus* antigens elicit a Th2 response in BALB/c mice with increase in IL-4, IL-5 and IgE production and accumulation of eosinophils [14,15]. *A. fumigatus* CD4⁺ clones are Th2 or Th0 [16–18]. When Asp-f-2-specific T cell clones from peripheral blood of ABPA patients are stimulated with rAsp f 2 a predominant Th2 (IL-5 synthesis) or a mixed Th1/Th2 response (IL-4, IL-5 and IFN- γ) is found [19]. Asp-f-1-specific T-cell lines obtained from peripheral blood of ABPA patients secrete abundant levels of IL-4 in an autocrine fashion and Asp f I-stimulated lymphoproliferation is inhibited by antibody blocking of IL-4, while no production of the Th1-associated cytokines IFN- γ or IL-2 is present [20]. Peripheral blood mononuclear cells (PBMCs) derived from ABPA patients show an increased sensitivity to IL-4 with an upregulation of the low-affinity IgE receptor on B cells compared to atopic and non-atopic control patients [18,21,22]. Higher amounts of the Th2 cytokines IL-4 and IL-5 are found in bronchoalveolar lavage fluid (BALF) of ABPA patients, whereas IL-2 and IFN- γ are decreased compared to controls [23]. *A. fumigatus* elicits the production of IL-10 which in turn may play an important role in T-cell tolerance and suppression of inflammatory and antifungal responses [24–26].

Is cystic fibrosis a Th2 disease by itself?

The occurrence of ABPA in CF and asthma patients suggests that both disease groups are susceptible towards ABPA due to a skewed Th1/Th2 immune response. In allergic asthma, the Th1/Th2 imbalance is indisputable, but for CF the Th1/Th2 immunological situation is not yet fully understood. Besides a favorable pulmonary microenvironment, including defective airway clearance and neutrophil insufficiency, there is emerging evidence that a Th1/Th2 imbalance might be of importance in CF [18,27].

Several lines of evidence suggest an underlying Th2 bias in CFTR^{-/-} lymphocytes [28,29]. CFTR knockout mice were found to develop a more profound lung inflammation in response to *A. fumigatus* hyphal Ag exposure compared to wild-type (WT) mice [28]. These CFTR-deficient mice also displayed an enhanced Th2 immune response to *A. fumigatus*, characterized by elevated IL-4 in the lung and IgE and IgG1 in serum. On a cellular level, CD4⁺ T cells from CFTR-deficient

mice produced higher levels of IL-4 and increased nuclear factor of activated T cells (NFAT) activation in response to T cell receptor (TCR) activation than wild-type CD4⁺ T cells. These results suggest that the CFTR defect in CF patients by itself might be involved in the Th2 immune bias, thereby favoring the development of an overwhelming Th2 disease in ABPA in CF patients. In accord with these findings, Moss *et al.* demonstrated that CF mononuclear cells isolated from CF patients showed a selective cytokine dysregulation after Phorbol-1,2-myristate-1,3-acetate (PMA)/TCR stimulation compared to healthy control cells, i.e., reduced IFN- γ secretion and increased IL-10 mRNA [29]. Furthermore, an impaired inducible nitric oxide synthase 2 (NOS2) and STAT1 signalling was detected in CF epithelium [30–32].

An alternative approach suggests that chronic *Pseudomonas aeruginosa* infection, the most common bacterial infection present in CF patients beyond infancy, shapes the pulmonary immune response towards a Th2 phenotype. Accordingly, higher percentages of CCR4⁺CD4⁺ Th2 cells, higher levels of the Th2 cytokines IL-4 and IL-13, higher levels of the Th2 chemokine thymus- and activation-regulated chemokine (TARC/CCL17) and lower levels of IFN- γ were found in the BALF in *P. aeruginosa*-infected CF patients compared to CF patients without chronic *P. aeruginosa* infection [33]. An association between *P. aeruginosa*-infection and the susceptibility towards Th2 responses in CF is corroborated by a recently published study demonstrating that sensitization to *A. fumigatus* in children with CF was preceded in the majority of patients by *P. aeruginosa* infection [34].

Another possible explanation for the putative Th2 shift in CF could be related to the CFTR-dependent impairment of the airway surface liquid (ASL) in CF epithelial cells [35]. The decreased ASL resulting in disabled mucociliary clearance might facilitate the interaction between sub-epithelial dendritic cells (DCs) and bronchopulmonary antigens, thereby leading to enhanced antigen presentation by DCs to T cells, initiation of Th2 responses and manifestation of allergic responses [36]. However, this intriguing hypothesis has to be tested in experimental models.

To summarize, there exists some evidence of an underlying Th2 bias in CF patients, potentially enhanced by chronic pulmonary *P. aeruginosa* infections, which may provide a favourable microenvironment for the Th2-associated lung diseases provoked by *A. fumigatus* and finally resulting in ABPA lung disease. However, the number of studies on Th1/Th2 in CF is limited and further *in vitro*, animal as well as human studies are warranted to investigate this issue.

The manifestation of clinically active ABPA is further supposed to be influenced by the underlying genotype. Accordingly, six different HLA-DR alleles [16,37] and polymorphisms in the IL-4 α receptor chain [38], the promoter region of the IL-10 [39] and in the collagen region of surfactant protein A2 [40] have been associated with the occurrence of ABPA. Assuming an impact of genetic risk factors for the development of ABPA might implicate a gradual spectrum of clinical presentations. This may explain why CF patients with *A. fumigatus* sensitization, elevated specific and total IgE but without ABPA were reported to have more rapid deteriorations in lung function [34,41].

The role of chemokines in allergic bronchopulmonary aspergillosis

Chemokines

Chemokines are a group of chemotactic cytokines that attract leukocytes through their corresponding G-protein coupled receptors to sites of inflammation [42]. Chemokines and chemokine receptors are termed according to their first cystein residues into C, C-C, C-X-C and CX₃C chemokines with C-C and C-X-C as the two largest families. Furthermore, chemokines can be separated into homeostatic and inflammatory chemokines, depending on whether they play mainly a role in basal immune cell trafficking (homeostatic chemokines) or are produced and released upon inflammation (inflammatory chemokines) to recruit leukocytes to the site of action [43,44].

Chemokine receptors were found to be preferentially expressed on Th1 or Th2 lymphocytes and are therefore classified as Th1 and Th2 associated chemokines and chemokine receptors [45]. According to this concept, Th2 cells express preferentially the CC chemokine receptors CCR3 [46], CCR4 and CCR8 [47], which are attracted by their specific ligands CCL11 (CCR3), CCL17 (CCR4), CCL22 (CCR4) [47,48] and CCL1 (CCR8), whereas Th1 cells express preferentially CCR5 and CXCR3 which are attracted by CCL5 (CCR1, 3, 5), CCL3 (CCR1, 5), CCL4 (CCR5) and CXCL10 (CXCR3), CXCL9 (CXCR3) and CXCL11 (CXCR3).

Chemokines have been involved in various Th2-mediated human diseases such as allergic asthma [49–53], atopic dermatitis [54–56] and other non-atopic diseases [44,57,58]. Despite a considerable number of studies found increased levels of CCL17 and CCL22 [33,54,55,59–69] as well as increased percentages of CCR4⁺ T cells [61,70–73] in peripheral blood and/or the airways from patients with allergic asthma and other atopic diseases, the functional significance of

CCR4 in allergic inflammation remains still controversial since animal studies revealed inconsistent results. While airway hyperresponsiveness (AHR) was attenuated in CCR4^{-/-} mice compared to CCR4^{+/+} mice in a model of *A. fumigatus* asthma [74], antibody blocking of CCR4 in a guinea pig asthma model resulted in only minor changes in numbers of CCR4⁺ T cells in the BALF and failed to inhibit the production of CCL11 (eotaxin), CCL22 or the recruitment of inflammatory leukocytes to the airways [75]. A further study using CCR4 knockout mice showed no significant differences in OVA-induced bronchial hyperreactivity, eosinophilia or OVA-specific Ig titers [76]. In contrast to blocking or deleting CCR4, studies using neutralization of the CCR4 ligands CCL17 and CCL22 showed a protective effect on OVA-induced airway eosinophilia, AHR and Th2 cytokine levels [77–81]. Thus, both human and animal data on CCR4 ligands point to a crucial role for CCL17 and/or CCL22 in allergic inflammation. However, the functional contribution of CCR4 in murine allergic asthma is less clear. What are the underlying reasons for this discrepancy? One explanation might be that CCR4 is not the only receptor for CCL17 and/or CCL22. This contention is supported by the finding that CCL17 can bind also to CCR8 [78] and CCR8 knockout mice showed an impaired Th2 cell response and eosinophil recruitment [82]. However, other studies could not confirm these findings [83,84]. In addition, the existence of an alternative receptor for CCL22 has been postulated [76]. Since CCR4 plays a role in thymic maturation [85] and regulatory T cells express CCR4, which is critical for their recruitment [86], the genetic deletion of CCR4 has probably more profound effects on the immune system than just affecting Th2 cell responses. Regarding animal models of allergic asthma and the effect of CCR4 knockout, the strong impact of CCR4 in *A. fumigatus*-induced asthma [74] in contrast to OVA-elicited asthma [76] points towards a distinct role of the CCR4 axis in fungal asthma [87]. Finally, differences between mouse and man might exist; however this is not very likely since high interspecies homologies of CCR4 and CCL17/CCL22 have been postulated. Future studies are necessary to assess the functional role of the CCL17/CCL22-CCR4/CCR8 axis in murine and human allergic inflammation to evaluate their therapeutic potentials.

Chemokines in allergic aspergillosis: a predominant role for CCR4 ligands?

Gene expression profiling revealed a number of cytokine- and chemokine-related genes including CCR4, CCR5 and CCL27 that were upregulated in a mouse

model of acute ABPA compared to control mice [88]. Furthermore, pulmonary concentrations of CCL2, CCL3, CCL5, CCL6, CCL11, CCL17, CCL22 and CXCL1 were increased during experimental fungal asthma [74,89]. Strong evidence for an involvement of chemokines in ABPA exists for CCR4 and its ligands [87]. Levels of CCL17 and CCL22 are highly elevated after conidia challenge in *A. fumigatus*-sensitized CCR4^{+/+} mice. CCR4^{-/-} mice show an increased anti-fungal immune response characterized by enhanced neutrophil function and augmented macrophage recruitment. In addition, CCR4^{-/-} mice have a reduction in bronchoalveolar and peribronchial eosinophilia and a limited chronicity of AHR [74]. Whole lung levels of IL-4 and IL-5 are increased in CCR4^{-/-} mice at day 3 after conidia challenge, whereas IL-4, IL-5 and IL-13 are lower compared with their wild-type counterparts. However, no differences in collagen deposition or peribronchial fibrosis are found between lungs from CCR4-deficient mice and control mice, suggesting that airway remodelling was not affected by CCR4-mediated pathways. Despite the lack of involvement of CCR4 in remodelling features during allergic aspergillosis, the rapid clearance of fungal material in the absence of CCR4 renders CCR4 and its ligands, CCL17 and CCL22 to pathophysiological and therapeutical relevant players and attractive future targets in ABPA.

Inspired by these findings in animal models, two clinical studies analyzed the value of chemokine levels for the diagnosis and follow-up of ABPA in CF patients [62,65]. The first study [62] at the CF Center of the University of Munich, Germany, demonstrated that serum levels of CCL17 were able to differentiate CF patients with ABPA compared to CF patients with *A. fumigatus* colonization or sensitization and healthy control subjects. In a longitudinal study, CCL17 serum levels peaked at ABPA exacerbations and indicated exacerbations more clearly than total IgE serum levels did. Corticosteroid treatment was associated with a decrease of CCL17 serum levels in CF ABPA patients. The second study [65] at the CF Center of the University of Berne, Switzerland, including a different CF patient cohort, compared the diagnostic value of several potential ABPA serum markers, namely total IgE, specific *A. fumigatus* IgE and IgG, recombinant *A. fumigatus* allergens f1, f3, f4 and f6 and CCL17. This study reproduced the finding from the first study that CCL17 serum levels were significantly increased in ABPA patients compared to atopic CF patients without clinically active ABPA. Receiver operating characteristic (ROC) curves revealed that CCL17 was superior to other markers for diagnosis of ABPA. The sensitivity,

specificity and diagnostic accuracy were higher for CCL17 than for total IgE, rAsp f4 or f6. When ABPA and non-ABPA patients were matched in the nested matched case-control design for same total serum IgE levels, CCL17 serum levels were still higher in the ABPA group compared to the non-ABPA group, suggesting that underlying atopic disease cannot simply explain the high CCL17 levels found in ABPA patients and points towards *A. fumigatus*-dependent factors. In the second study it was also observed that several ABPA patients showed increased CCL17 serum levels already up to three years before their clinical diagnosis of ABPA. Despite these promising results, these both studies also revealed that the quantitation of CCL17 serum levels is influenced by methodological issues as shown by the considerably high inter-assay variability observed in the second study [65]. Further clinical studies involving a representative number of CF patients are necessary to evaluate the practical value of CCL17 serum levels in the diagnosis and follow-up of ABPA in CF patients. The role of polymorphisms in the CCL17 gene [90] on serum levels and their possible impact on the clinical course of CF/ABPA patients remains to be determined.

Based on these findings we propose the following scenario how *A. fumigatus* encounters the pulmonary immune system and how this invidious liaison in CF patients may trigger an overwhelming Th2 immune response which finally results in ABPA lung disease [87]. *A. fumigatus* conidia are recognized via pattern-recognition receptors (PRR), namely TLRs [91,92] and the β -glucan receptor dectin-1 on dendritic cells (DC), alveolar macrophages (AM) and lung epithelial cells [91,93]. Among Toll-like receptors (TLRs), in particular TLR2 [94,95], TLR4 [96,97], or an interaction between TLR2, TLR4 and TLR9 via MyD88 [93] are considered to play a crucial role in the recognition of *A. fumigatus* by the innate immune system. *A. fumigatus* proteases facilitate the penetration through the epithelial layer [98,99]. DCs initiate disparate Th1 or Th2 responses after encounter with *A. fumigatus* in the murine airways [100]. DCs represent a major source of CCL17 and CCL22 [101,102]. Thus it is tempting to speculate that *A. fumigatus* might direct DCs towards the secretion of CCL17. In addition, the tryptophan catabolism via indoleamine 2,3-dioxygenase (IDO) may be involved in the induction of DC-dependent regulatory effects and tolerance to *A. fumigatus* [103,104].

Based on the current knowledge on the biological role of CCL17 and CCR4 we propose five distinct ways how CCL17 might modulate the pulmonary immune response in ABPA:

- i. CCL17 attracts via CCR4 Th2 cells that initiate and sustain the allergic lung disease in ABPA and are also able to antagonize Th1 cell-mediated host defense responses [105].
- ii. Besides Th2 cells, regulatory T cells express CCR4 and migrate to CCL17 [86]. Montagnoli *et al.* demonstrated that regulatory T cells have distinct roles in regulating the inflammation and allergic responses associated with *A. fumigatus* [106]. The increased expression of CCL17 during ABPA may promote the excess accumulation of regulatory T cells in the pulmonary environment. Given the marked ability of these cells to generate IL-10 and TGF- β , the presence of regulatory T cells in the *A. fumigatus*-infected lung could be deleterious to the development of effective immunity by dampening anti-fungal Th1 responses. On the other hand, CCR4⁺ regulatory T cells may be recruited to counterbalance the overwhelming Th2 inflammation.
- iii. AMs are considered as potent killers of *A. fumigatus*. Besides its effect on T cells, data suggests that CCL17 may have a direct, inhibitory effect on the activation and antibacterial capacity of macrophages [74]. The inhibitory effect of CCL17 appears to alter the synthesis of Th1-associated mediators such as TNF- α , IL-12, CCL3, CCL5, CXCL10 and CXCL13 by AMs [107] which exert prominent immunostimulatory anti-fungal effects [108]. Given the recent evidence that dectin-1 plays a critical role in the recognition and internalization of *A. fumigatus* conidia [109,110], CCL17 may exert its immunomodulatory effect via control of the expression of dectin-1 or other PRR receptors such as TLR2 or TLR4 on AMs [91,92].
- iv. Th17 cells represent a lineage distinct from Th1 and Th2 cells producing IL-17 and IL-22 [111,112]. Recent evidence suggests that Th17 cells express CCR4 [113]. Based on the elevated levels of IL-17A and IL-17F in CF airway fluids [36] and the proposed role for Th17 as interface between T cell and neutrophil inflammation in CF lung disease, the recruitment of Th17 via CCR4/CCL17 may play an important role in ABPA lung disease.
- v. Invariant CD1d-restricted natural killer (iNKT) cells express CCR4 on their surface which was found to be critical for the localization of these cells to the airways and to induce airway hyperreactivity [114]. Thus, high levels of CCL17 may recruit iNKT cells to the lungs in ABPA.

In summary, enhanced CCL17 levels in ABPA have the potential to markedly alter the innate immune mechan-

isms that normally work so effectively to prevent the growth of *A. fumigatus* in the pulmonary environment. Dampen the overwhelming Th2 immune response in ABPA patients, in particular CCL17/CCR4, might be pivotal to repair the impaired Th1/Th2 immune balance in CF patients with ABPA. Kawasaki *et al.* demonstrated that treatment of ovalbumin sensitized mice with anti-CCL17 antibodies before challenging with aerosolized ovalbumin led to decreased percentages of infiltrating CD4⁺ lymphocytes and decreased levels of Th2 cytokines compared to untreated mice [77]. CCL17 inhibitors provide a promising tool to inhibit the strong Th2 immune response in ABPA patients, but no studies in humans have been performed thus far.

Open questions

Several questions on the mechanisms behind the cystic fibrosis-ABPA link remain unanswered and should be addressed in future studies:

1. *Underlying Th1/Th2 imbalance in CF*
 - i. Is a Th1/Th2 imbalance consistently found in CF patients or restricted to a subgroup of CF patients. If so what defines this subgroup?
 - ii. Are CF patients with an underlying Th2 bias those who develop ABPA?
 - iii. Is the Th2 shift in CF patients related to the genetic defect in the cystic fibrosis transmembrane regulator (CFTR) gene? If so, what is the cellular link between CFTR and Th2 responses (NFAT?)?
 - iv. Is the Th2 shift in CF due to *P. aeruginosa* infection?
2. *Chemokines & immunological mechanisms*
 - i. CCL17/CCR4: Have CCL17 serum levels a predictive value for the occurrence of ABPA in CF patients? Are CCL17 serum levels in CF patients influenced by SNPs in the 5'-flanking region (-431C>T) of the CCL17 gene as suggested recently in healthy and atopic individuals [115]? Which CCR4⁺ cells (Th2, Treg, Th17, iNKT cells, others?) accumulate in the circulation or the lungs of ABPA patients and what is their functional role?
 - ii. Regulatory T cells: The association of polymorphisms in the promoter region of the IL-10 with ABPA in CF patients [39] and the well-known role of regulatory T cells as IL-10 producers points towards a role for these cells in ABPA. However, the role of regulatory T cells in the pathogenesis of ABPA has been

addressed by only a few studies. Montagnoli *et al.* and Romani *et al.* demonstrated the involvement of CD4⁺CD25⁺ Tregs, Thymosin alpha1, IL-10, CTLA-4, TLR9, type I interferon receptor signaling and the immuno-suppressive IDO pathway in the balance between allergic and tolerogenic immune responses in allergic aspergillosis in mice [104,106]. The relevance of these mechanisms for human ABPA remains to be established. Furthermore, the role of CCL17 in attracting CCR4⁺ Tregs remains unclear as discussed above.

- iii. Th17 cells: IL-17 stimulates granulopoiesis in mice and increased levels of IL-17A and IL-17F are found in CF sputum fluids, suggesting an involvement of Th17 cells in CF lung disease [36,116–119]. The role of IL-17/IL-22 was recently underlined by the finding that IL-22 mediates mucosal host defense against Gram-negative bacterial pneumonia and lymphocytes isolated from human explanted lymph nodes produced higher amounts of IL-17A and IL-22 than cells from control subjects [120]. Since Th17 cells express CCR4, these cells may accumulate in ABPA, but so far the functional role of Th17 cells in CF as well as ABPA has not been addressed.

Conclusions

ABPA in CF patients is a devastating disease which requires early diagnosis and subsequent treatment. The Th2 chemokine CCL17 was found to be useful in the diagnosis and longitudinal follow-up of ABPA in CF patients and might therefore represent a biomarker and future therapeutic target in ABPA. The complex network between genetic susceptibility, CF-associated Th1/Th2 imbalance, CCL17, DCs and regulatory T cells may cooperatively determine the manifestation of ABPA lung disease. Despite intriguing insights into the immunological links between ABPA and CF, further experimental and clinical studies are needed to better understand the role of CCL17 and other immunological mechanisms in the pathogenesis, diagnosis and treatment of ABPA in CF patients.

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