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REVIEW

Role of interleukin-17F in chronic inflammatory and allergic lung disease

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Summary

IL-17 family members belong to a distinct category of cytokines that coordinate local tissue inflammation by inducing the release of pro-inflammatory and neutrophil-mobilizing cytokines. The importance of the IL-17 family in inflammatory and autoimmune disease is becoming increasingly apparent. IL-17F is a recently discovered member of the IL-17 family that has a number of biological activities through induction of various cytokines, chemokines, and mediators. IL-17A, the founding member of the IL-17 family, and IL-17F are produced by several inflammatory cells, including activated T cells, in response to infectious and antigenic stimuli. Overexpression of IL-17A or IL-17F in the lungs results in induction of CXC chemokines and neutrophil recruitment. In a case–control study of 1125 unrelated Japanese subjects, a His161 to Arg161 (H161R) substitution in the third exon of the IL17F gene was shown to be associated with asthma and chronic obstructive pulmonary disease (COPD). Functionally, this variant failed to induce cytokines and chemokines, and interestingly, was able to antagonize the activity of wild-type IL-17F. These results provide an experimental basis for the observed genetic association with chronic inflammatory lung diseases, and also suggest the potential therapeutic utility of this antagonistic variant of IL-17F. Given that asthma and COPD are complex diseases involving a number of genetic and environmental factors, the genetic impact of IL-17F H161R with regard to the development of chronic airway inflammation likely varies among individuals with different genetic backgrounds and environmental exposures.

Keywords asthma, atopy, COPD, IL-17F
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Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are inflammatory conditions of the lung associated with structural alterations [1], which exhibit distinct patterns of airflow obstruction. For example, when lung tissue from non-smokers with mild asthma is compared with that of smokers with mild to moderate COPD, different patterns of infiltration by inflammatory cells and different structural changes are observed [2]. As the diseases progress and higher doses of corticosteroids are required, the inflammatory patterns of asthma and COPD become harder to distinguish from one another. Increased infiltration of the airway with neutrophils characterizes lung inflammation in COPD and severe asthma [3–5] and, not surprisingly, neutrophilia is often associated with disease severity [6] and chronic airway narrowing [5]. Neutrophils are believed to contribute to tissue damage through the release of granule proteins and reactive oxygen metabolites, as well as pro-inflammatory and pro-fibrotic cytokines. In addition to causing direct tissue damage, neutrophil-derived pro-inflammatory mediators can perpetuate inflammation, resulting in chronic changes in airway function [7].

Recent progress in molecular and functional studies of IL-17F has provided evidence for its role in pulmonary neutrophilia through the induction of CXC chemokines [8]. Furthermore, evidence from our genetic analysis of the IL17F gene has suggested a potential role of the sequence variant in regulation of the disease process [9]. These findings, together with published reports regarding another member of the IL-17 family, IL-17A, suggest the importance of this new cytokine family in mediating the migration and activation of inflammatory cells, and collectively perpetuating the chronic airway inflammation that typifies asthma and COPD. This review provides a

brief synopsis of recent findings regarding these two chronic inflammatory and often debilitating diseases.

The interleukin-17 family and interleukin-17F

IL-17A, a prototype of the IL-17 family, was first cloned more than 10 years ago [10], and has been shown to contribute to innate immunity and various host-defence mechanisms. Recently, five other members (IL-17B-F) of the IL-17 family have been described [11–14]. The IL-17 family shares five distinct cysteine residues, which are unique to the IL-17 family. IL-17F, a protein containing 153 amino acids, is approximately 50% homologous with IL-17A, more so than with any other members of the IL-17 family [14, 15]. Genes encoding IL-17A and IL-17F lie next to each other on chromosome 6 [15] and likely arise from a gene duplication event.

IL-17A is produced by activated $CD4^+$ T cells, $CD8^+$ T cells, and eosinophils. In mice, a unique subset of T cells has recently been found to exclusively express IL-17A and IL-17F [16, 17], but not IL-4 or IFN-γ. The existence of this subset has not been confirmed in humans. Of note, while co-expression of IL-17A and IFN-γ (Th1/Th0 phenotype) has been found in T cells from the synovial fluid of patients with rheumatoid arthritis (RA) [18], analysis of nickel-specific $CD4^+$ T cell clones isolated from peripheral blood or skin lesions from patients with allergic contact dermatitis shows expression of IL-17A in both Th1 and Th2 cells [19].

IL-17A targets fibroblasts, vein endothelial cells, and airway epithelial cells, and induces the production of various cytokines and mediators [20]. IL-17A has been found to be associated with a number of diseases, including asthma, COPD, systemic lupus erythromatosis, RA, and cancer [21]. Although a comprehensive comparative analysis of IL-17F and IL-17A has not been performed, IL-17F appears to have biological actions similar to IL-17A both *in vitro* and *in vivo* [22, 23]. IL-17F induces various cytokines, chemokines, and adhesion molecules, including IL-6, IL-8, GROα, ENA-78, transforming growth factor-β (TGF-β), MCP-1, G-CSF, granulocyte macrophage-colony forming factor (GM-CSF) and intracellular adhesion molecule-1 (ICAM-1), in airway epithelial cells, vein endothelial cells, and fibroblasts [14, 15, 22–24]. Of note, IL-17F significantly induces the expression of ICAM-1 in primary bronchial epithelial cells [14], while IL-17A fails to induce its expression. Furthermore, in addition to Th1 and Th2 cells, activated human mast cells and basophils express IL-17F [14], suggesting a wider role of IL-17F in inflammatory responses. Expression of the *IL17F* gene also shows a wider tissue distribution than *IL17A*, with marked expression of *IL17F* in the human liver, lung, and fetal liver tissue, unlike *IL17A* [14].

Role of interleukin-17F in chronic inflammatory lung diseases

A recent study has shown increased expression of the *IL17F* gene in patients with allergic asthma in response to allergen challenge [14]. In contrast, no *IL17A* transcripts were detected in these patients following allergen challenge. In an animal model of asthma, overexpression of IL-17F enhanced antigen-induced allergic inflammation, including airway responsiveness, goblet cell hyperplasia, and mucin gene expression, all of which contribute to allergic inflammation and airway remodelling [8]. Lung tissue from IL-17F-transduced mice showed substantially increased levels of inflammatory cytokines and chemokines, including IL-6, IFN-γ, inflammatory protein 10 (IP-10), and monokine, induced by IFN-γ, insulin-like growth factor-1, and C10. Some of these molecules induce lung fibrosis and airway remodelling [25, 26], suggesting a potential role of IL-17F in airway remodelling related to chronic inflammatory lung diseases, such as asthma and COPD.

The number of $CD4^+$ T cells increases along with neutrophil infiltration in the airways of patients with asthma [27]. In animal models of asthma, pre-treatment with anti-$CD4^+$ antibody significantly suppresses airway neutrophilia and eosinophilia [28], suggesting regulation of neutrophil infiltration by $CD4^+$ T cells in asthma. Also, there is an association between accumulated $CD4^+$ and $CD8^+$ T cells within airway tissue samples and airway neutrophilia in patients with COPD [29]. It is therefore conceivable that activation of IL-17A- and IL-17F-mediated pathways might provide a link between local activation of T cells and sustained accumulation of neutrophils in inflamed airways.

Genetic analysis of interleukin-17F H161R with regard to asthma and chronic obstructive pulmonary disease

The *IL17F* gene is 7742 bp in length and contains three exons [30]. An analysis of the relationship between *IL17F* gene polymorphism and asthma and COPD revealed an association between a sequence variant (H161R) in the third exon of the *IL17F* gene and the development of asthma or COPD in a panel of 435 healthy controls (199 non-atopic and 236 atopic) and 432 patients with asthma (111 non-atopic and 321 atopic), as well as 258 patients with COPD (196 non-atopic and 62 atopic) [9] (Table 1). We defined atopy as a positive response to at least one of 10 commonly inhaled allergens, including *Dermatophagoides farinae* (Der f), grass pollens, animal danders, and moulds.

A genotype-based χ^2 association analysis indicated a significant association between the H161R variant and asthma ($P = 0.0028$) [9] (Table 1). Importantly, none of the asthmatic subjects were homozygous for H161R. The odds

ratio (OR) for asthma was 0.06 (95% confidence interval, 0.01–0.43, $P = 0.0039$) among H161R homozygotes, compared with wild-type homozygotes (Table 2). Heterozygosity for the H161R allele was not associated with asthma, compared with wild-type (His161) homozygotes [OR = 1.32 (0.95, 1.84), Table 2]. Significant differences in H161R frequency were not observed among controls and patients with COPD (Table 1). We then combined bronchial asthma and COPD into a single category to examine whether association of this variant with these lung diseases can be found. When the results were stratified according to atopic status, the H161R variant was significantly associated with these two diseases, especially among atopic subjects (Table 2). In atopic patients with asthma, pre-bronchodilator baseline FEV1/FVC values also showed a significant association with the H161R variant (Fig. 1). However, in a recent study of African American and Caucasian subjects [30], Ramsey et al. failed to find evidence of associations between asthma and any of the *IL17F* polymorphisms, including the H161R variant. This discrepancy may be due to the fact that the H161R variant is more frequent among Japanese subjects than the European American population (11.4% vs. 4.5%). Conversely, we observed the 1165G/7488T haplotype less frequently among a Japanese population (19.5%) than a European American population (51.4%). This suggests that the degree of linkage disequilibrium differs between these two populations, which may explain the discordant results regarding the presence of a genetic association in these two studies. Furthermore, information about atopic status was not provided in the study by Ramsey et al, which may be important in examining a potential genetic association, given our results indicating a greater genetic impact in atopic subjects.

Allergen challenge clearly induces gene expression of *IL17F* in human asthmatic airways [14]. In addition, overexpression of the *IL17F* gene in an animal model of allergic asthma enhances Ag-induced airway inflammation, goblet cell hyperplasia, and mucin gene expression [8]. These findings, together with the observed association between the H161R variant and disease phenotype in atopic individuals, suggest that IL-17F may potentiate allergen-induced airway inflammation. Thus, there may be a complex interaction between environmental and genetic factors in the development of asthma, such that different pathways produce asthma in atopic and non-atopic individuals.

Table 1. Subject characteristics and genotype information

	Healthy control	Asthma	COPD
N	435	432	258
Sex (m/f)	282/153	197/235	243/15
Age (median, range)	36 (18–72)	47 (16–79)	71 (41–87)
Never smoked (%)	69.7	56.1	0
Atopy (%)	54.5	74.3	23.9
IgE (logIU/ml) (mean SD)	1.85 (0.63)	2.37 (0.67)	1.77 (0.69)
Eosinophils (logNumber)		2.49 (0.45)	2.21 (0.33)
FEV1 %predicted (SD)		75.5% (2.33)	57.2% (2.24)
IL17F 7899 T > C (H161R)			
TT	347	332	204
TC	79	100	51
CC	9	0	3

COPD, chronic obstructive pulmonary disease.

Table 2. Genetic impact of the H161R variant on asthma and COPD

	Asthma		COPD		Asthma+COPD	
H161R	OR	95% CI	OR	95% CI	OR	95% CI
All subjects ($n = 1125$)						
His/His	1	Ref.	1	Ref.	1	Ref.
His/Arg	1.32	0.95–1.84	1.1	0.74–1.63	1.24	0.91–1.68
Arg/Arg	0.06†	0.01–0.43	0.57	0.15–2.12	0.22†	0.06–0.8
Atopic subjects ($n = 619$)						
His/His	1	Ref.	1	Ref.	1	Ref.
His/Arg	1.42	0.92–2.19	2.06	1.08–3.94	1.52	1.0–2.3
Arg/Arg	0.06*	0.01–0.49	0.34	0.04–2.84	0.05†	0.01–0.41
Non-atopic subjects ($n = 506$)						
His/His	1	Ref.	1	Ref.	1	Ref.
His/Arg	1.31	0.75–2.27	0.81	0.49–1.35	0.98	0.63–1.53
Arg/Arg	0.27	0.03–2.42	0.98	0.19–4.94	0.64	0.13–3.23

*$P < 0.01$,

†$P < 0.005$.

COPD, chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval.

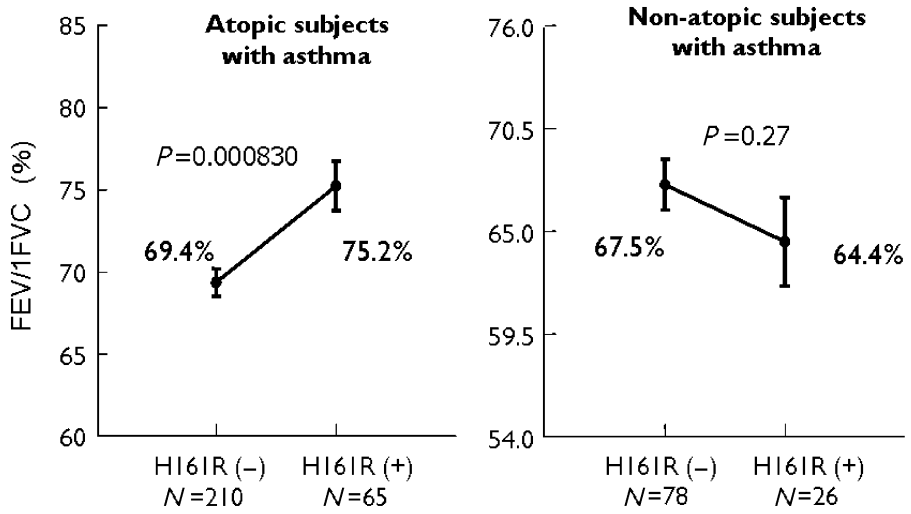

Fig. 1. Association between pre-bronchodilator baseline FEV_1/FVC values and H161R in patients with asthma. Patients with atopic asthma and the H161R variant (associated with dysfunctional IL-17F) had greater pre-bronchodilator baseline FEV_1/FVC measurements than subjects without the variant. FEV_1/FVC measurements were 69.4% (SD 12.0, $n = 210$), 75.2% (12.2, $n = 65$), 67.5% (12.0, $n = 78$), and 64.4% (12.1, $n = 26$), for atopic asthmatics without H161R, atopic asthmatics with the variant, non-atopic asthmatics without the variant, and non-atopic asthmatics with the variant, respectively. FEV_1, forced expiratory volume at 1 s; FVC, forced vital capacity.

The impact of a viral infection in atopic subjects on airway inflammation may be influenced by the presence of H161R. A previous study [31] demonstrated increased airway epithelial mucus production among pre-sensitized RSV-infected (OVA/RSV) mice, compared with OVA mice 14 days after infection, while almost no mucus production was observed in mice that were only RSV infected. Although they did not find an increase in type 2 cytokine production in OVA/RSV mice, compared with OVA mice, they found a significant association between increased gob-5 and Muc5ac expression in OVA/RSV mice and increased IL-17A levels in the lung.

Functional study of an H161R variant of interleukin-17F

To examine whether mutant IL-17F (H161R) with a non-synonymous substitution is a functional variant of wild-type IL-17F, an analysis of IL-17F-mediated signalling and subsequent induction of cytokine and chemokine expression was performed using a bronchial epithelial cell line, BEAS-2B, as a model [9]. Activation of the Raf1-MEK1/2-ERK1/2 pathway, known to be involved in IL-17F-mediated signalling in bronchial epithelial cells [32], was first examined. Unlike wild-type IL-17F, mutant IL-17F did not induce activation of Raf-1, MEK1/2, and ERK1/2, in bronchial epithelial cells [26]. While wild-type IL-17F induced a significant increase in cytokine (GM-CSF) and chemokine (IL-8, GROα, and ENA-78) levels 24 and 48 h after stimulation, mutant IL-17F did not induce expression of these proteins [9]. This loss of IL-17F function was not due to an inability to bind to the IL-17F receptor as mutant IL-17F blocked wild-type IL-17F-induced IL-8 production in a dose-dependent manner [9]. This suggests that mutant IL-17F may be a naturally occurring antagonist of wild-type IL-17F, and that its antagonizing activity may provide therapeutic benefit (Fig. 2).

To date, the receptor for IL-17F has not been identified, but indirect evidence suggests a distinct cognate receptor [9, 15]. In a recent meeting report, IL-17F was shown *in vitro* to bind to IL-17RC, a distinct receptor from IL-17R [33]. However, while antibodies specific for the IL-17R significantly attenuate the release of either IL-17A- or IL-17F-induced chemokines, the soluble form of IL-17R inhibits the activity of IL-17A, but not IL-17F, in bronchial epithelial cells [34], suggesting the presence of a distinct receptor or co-receptor for IL-17R in IL-17F-mediated responses. Further work is needed to elucidate the nature of the receptor for IL-17F. The crystal structure of IL-17F was recently elucidated, and IL-17F is believed to form a disulphide-linked homodimer [15], composed of two pairs of antiparallel β-strands. The H to R substitution at residue 161 is closer to the C-terminal end of the IL-17F sequence, which does not reside in the β-strand structure. While the structural basis for antagonism by mutant IL-17F is unclear at present, the involved substitution is unlikely to alter the core conformation of the protein. Rather, it may influence its affinity of binding to the receptor.

Conclusion

IL-17F is a newly described cytokine involved in airway inflammation. The present case–control study demonstrates an association between an *IL17F* gene polymorphism and chronic inflammatory lung diseases, including

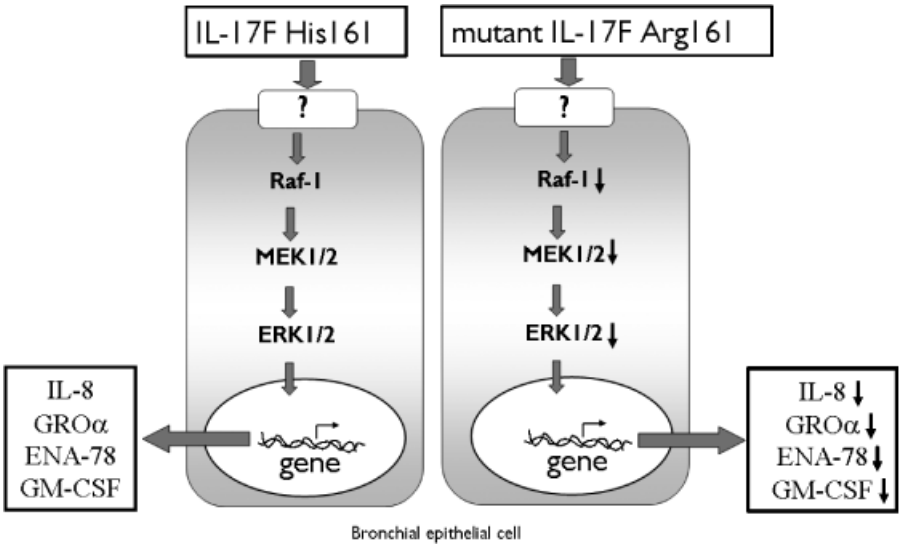

Fig. 2. Proposed functional consequences of the IL17F H161R variant. Mutant IL-17F was unable to activate the Raf1-MEK-ERK1/2 pathway, but antagonized wild-type IL-17F activity, suggesting that IL-17F is able to bind the receptor, but not activate the signalling pathway.

bronchial asthma and COPD, especially in subjects with atopy. Analysis of 1125 unrelated Japanese subjects revealed a significant association between a coding-region sequence variant, SNP rs763780 [7488T>C, resulting in a His to Arg substitution at position 161 (H161R)], and chronic inflammatory lung disease, suggesting that IL-17F is critically involved in the pathogenesis of chronic inflammatory lung diseases. *In vitro* functional studies further demonstrate that, compared with wild-type IL-17F, the H161R variant is unable to activate MAP kinase, as well as cytokine and chemokine production, in bronchial epithelial cells. Of significance, the H161R variant inhibits induction of IL-8 by wild-type IL-17F. These findings suggest a potential mechanism underlying the significant association observed between the IL-17F H161R variant and asthma and COPD. As chronic inflammation is thought to play a crucial role in deteriorating lung function, IL-17F may serve as a target for ameliorating the effects of neutrophil-mediated chronic airway inflammation. However, asthma and COPD are complex genetic diseases involving multiple genes and environmental factors. As such, it is unlikely that the IL-17F gene is a primary determinant of the chronic airway inflammation underlying asthma and COPD. Nevertheless, our findings may identify one gene in a common pathway mediating the development of asthma and COPD.

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