Allergology International (2003) **52**: 173–182

Review Article

Neutrophils, interleukin-17 and obstructive airway disease

Anders Lindén

Department of Allergology & Respiratory Medicine, Institute of Internal Medicine, Göteborg University, Gothenburg, Sweden

Abstract

There is increasing evidence that an exaggerated accumulation of activated neutrophils is linked to the clinical course of obstructive airway diseases, such as asthma and chronic obstructive pulmonary disease. The present review article focuses on the evidence that the T cell cytokine interleukin (IL)-17 plays a role in orchestrating the accumulation and subsequent activation of neutrophils in the airways and lungs. The mechanistic roles of neutrophils and IL-17 in obstructive airway disease are discussed. It is concluded that targeting IL-17 may consitute a potential strategy for developing novel pharmacotherapeutic interventions against obstructive airway disease.

Key words: airway inflammation, asthma, chemokine, chronic obstructive pulmonary disease, cytokine, eosinophil, macrophage, protease, T lymphocyte.

Introduction

There is now increasing evidence that the cytokine interleukin (IL)-17 (also named 'IL-17A') plays a pro-inflammatory role in the immune system; this evidence has emerged during the 10 years that have passed since the discovery of this intriguing cytokine.[1,2] The first study focusing on the effects of IL-17 protein in the airways[3] has now been followed by several other studies that have improved the understanding of the biology of IL-17 and its potential role in airway inflammation. The present review focuses on the evidence that IL-17 plays a role in orchestrating the accumulation and subsequent activation of neutrophils in the airways and lungs.

Correspondence: Associate Professor Anders Lindén, Lung Pharmacology Group, Department of Respiratory Medicine & Allergology, Institute of Internal Medicine, Göteborg University, Guldhedsgatan 10A, SE-413 46 Gothenburg, Sweden.
Email: anders.linden@lungall.gu.se
Received 26 June 2003.

Accumulation of neutrophils in airway and lung disease

The accumulation and activation of neutrophils in the airways and lungs is linked to the course of several inflammatory diseases, including obstructive airway diseases, such as asthma and chronic obstructive pulmonary disease (COPD), and related conditions, such as non-specific bronchial hyperreactivity and chronic bronchitis.[4–19] The evidence cited has been obtained through characterization of the number of neutrophils present in airway and lung tissue, in bronchoalveolar lavage (BAL) fluid, in induced sputum and in blood.

Accumulation of neutrophils and function of airways and lungs

The number of neutrophils in the airway lumen correlates negatively with non-specific airway reactivity in patients with mild asthma.[19] Interestingly, the number of neutrophils in the airway lumen and mucosa also correlates negatively with lung function in smokers with or without chronic bronchitis or COPD.[10,15–17] Among smokers, the number of luminal neutrophils correlates positively with the annual decline in lung function.[20] It is also known that neutrophil recruitment is associated with bronchial hyperresponsiveness in rodent airways *in vivo*.[21] Thus, it is possible that the accumulation of neutrophils exerts a functional impact on the airways in asthma and COPD.

Neutrophils produce pathogenetically relevant compounds

The fact that neutrophils are capable of releasing bioactive compounds that can cause functional alterations in the airways and lungs is interesting because these functional alterations resemble those observed in obstructive airway diseases, such as asthma and COPD.

Neutrophil elastase is an example of a proteolytic enzyme that can be released from neutrophils in the airways. As indicated by its name, elastase degrades elastin, a structural component of the lungs, and it has been shown that the deposition of exogenous elastase in rodent airways leads to emphysema-like alterations in the lungs and tissue remodeling in the airways *in vivo*.[22–26] Neutrophil elastase also alters the structure of collagen gels *in vitro*.[26] Indeed, neutrophil elastase is a potent inducer of secretion by gland cells in rodent airways[27,28] and it can cause bronchial hyperresponsiveness in murine airways *in vivo*.[22,23] In view of these findings, it is of special interest that neutrophil elastase can be detected in obstructive airway disease.

Neutrophil elastase is detected in the submucosa of bronchi of patients with severe asthma, regardless of whether eosinophils are present.[9] Furthermore, even when there is no detectable airway infection present, the luminal concentration of neutrophil elastase is increased in severe asthma.[5–7] Similarly, an increased luminal concentration of elastase is observed in chronic bronchitis and COPD.[26] There is also evidence consistent with this elastase actually having a functional impact; the luminal concentration of this proteolytic enzyme correlates negatively with lung function in asthma and chronic bronchitis.[6]

Certain evidence puts forward some matrix metalloproteases (MMP) as neutrophil-derived compounds contributing to the pathogenesis of obstructive airway disease in the airway and lungs.[30,31] Thus, the luminal concentration of MMP-8 and -9 is increased in asthma and COPD, respectively.[30,32–34] Interestingly, the luminal concentration of MMP-8 correlates negatively with lung function in patients with asthma and MMP-9 appears to mediate allergen-induced airway hyperresponsiveness in sensitized rodents *in vivo*.[30,35]

In addition to proteolytic enzymes, neutrophils can produce oxygen free radicals and neutrophils from patients with asthma display increased production of these cytotoxic compunds.[36–38] There is also evidence that oxygen free radicals can induce the transcription of mRNA for neutrophil-recruiting cytokines, such as the neutrophil chemoattractant IL-8, leading to subsequent IL-8 protein release and perpetuation of neutrophil recruitment.[39,40] Hypotheticallly, these events may contribute to airway remodeling and altered lung function. In line with this, there is evidence that oxygen free radicals contribute to bronchial hyperresponsiveness and that this phenomenon involves neutrophils under certain conditions in mammals *in vivo*.[22,41–44] Furthermore, conditioned medium from human neutrophils can increase the reactivity of human bronchial smooth muscle *in vitro*, but it remains to be confirmed whether this particular effect is mediated by oxygen free radicals.[45]

Neutrophils can also perpetuate their own accumulation through the production and release of compunds that, *per se*, recruit even more neutrophils. These compounds include leukotriene B_4, tumor necrosis factor (TNF)-α and IL-8.[46–54] Interestingly, there is evidence to support that both TNF-α and IL-8 cause bronchial hyperresponsiveness in rodent airways *in vivo*.[40,55,56] It may be that this TNF-α perpetuates additional neutrophil recruitment via the stimulation of IL-8 in bronchial epithelial cells.[39,57,58] The fact that the luminal concentration of IL-8 correlates negatively with bronchial reactivity in patients with mild asthma[19] is, indeed, compatible with neutrophils exerting a functional impact in obstructive airway disease.

To summarize, there is evidence that neutrophils can contribute to gland hypersecretion, bronchoconstriction and bronchial hyperreactivity, as well as tissue destruction in lungs and aiway remodeling in obstructive airway disease. Neutrophils can also perpetuate the additional accumulation of neutrophils at the inflammatory site and this type of local accumulation of neutrophils seems to exert a functional impact on the airways and lungs. For these reasons, the endogenous mechanisms orchestrating the accumulation and activation of neutrophils constitute potential targets for novel pharmacotherapy.

Orchestration of neutrophils in the airways and lungs

A number of different cell types in the bronchial wall, airway lumen and post-capillary venules can release chemoattractant signals to neutrophils, such as IL-8 and other C-X-C chemokines. Thus, bronchial epithelial cells, bronchial smooth muscle cells, fibroblasts, macrophages/monocytes, neutrophils themselves and even eosinophils have the potential to contribute to neutrophil recruitment by releasing IL-8 in asthma and chronic

bronchitis.[39,57–63] It remains unknown how these cells are coordinated to orchestrate neutrophil accumulation, in particular because chemokines are believed to function by establishing concentration gradients.

T Lymphocytes and the accumulation of neutrophils

There is convincing evidence that certain T lymphocytes orhestrate the recruitment and activation of granulocytes in the airways and lungs, in particular for $CD4^+$ lymphocytes and eosinophilic granulocytes. Thus, in the airways of patients with newly diagnosed asthma, the total number of lymphocytes, eosinophils and neutrophils is increased.[64] Specific blockade of lymphocytes with an anti-$CD4^+$ antibody or an anti-IL-2 receptor antibody does prevent allergen-induced recruitment of eosinophils and neutrophils, respectively, in the airways of sensitized rodents *in vivo*.[65,66] In addition, in the airways of certain patients with COPD, there is an accumulation of both $CD4^+$ lymphocytes and neutrophils.[67,68] Furthermore, exposure to cigarette smoke causes an accumulation of $CD4^+$ lymphocytes and neutrophils in rodent airways *in vivo*.[69] The accumulation of $CD4^+$ lymphocytes also relates to functional changes in the airways; the presence of $CD4^+$ lymphocytes is related to bronchial reactivity in the airways of humans and rodents *in vivo*, even though it is not known whether this phenomenon relates to the orchestration of eosinophils, neutrophils or both.[70–72] Importantly, the mechanisms linking $CD4^+$ lymphocytes to the accumulation of neutrophils have remained unclear. This lack of knowledge about mechanisms is in sharp contrast with the vast knowledge about the mechanistic links between $CD4^+$ lymphocytes and eosinophils in the airways and lungs, where Th2 cytokines, such as IL-3, IL-4 and IL-5, as well as the growth factor granulocyte–macrophage colony stimulating factor (GM-CSF), are believed to play important roles.[73–77]

Production of IL-17 by T lymphocytes *in vitro*

The homodimer IL-17 is a 155 amino acid molecule with a molecular weight ranging from 15 to 22 kDa.[78] Rodent IL-17 displays a substantial structural homology with human IL-17: the glycosylation site is highly conserved, a fact that is compatible with IL-17 being important for the mammalian immune system.[78]

As judged from studies on spleen or blood cells *in vitro*, human and rodent $CD4^+$ lymphocytes can produce, and subsequently release, IL-17 protein when activated *in vitro*.[2,78,79] Of particular interest for inflammatory disease in the airways and lungs, it was recently demonstrated that $CD3^+$ lymphocytes from rodent lungs can produce free soluble IL-17 protein *in vitro*.[80] In line with IL-17 being produced by both $CD8^+$ and $CD4^+$ lymphocytes, memory T lymphocytes (CD45RO) of both these subsets may account for the production of IL-17 protein, as indicated in lymphocytes isolated from the blood of healthy human volunteers and studied *in vitro*.[81] It has also been claimed that IL-17 is produced mainly by the Th0 and Th1 lymphocyte subsets *in vitro*, based on findings in synovial $CD4^+$ cells from patients with rheumatoid arthritis.[82] In one study only, it has been claimed that eosinophils constitute a source of IL-17 protein, but to date there is no published functional evidence that eosinophils can release free soluble IL-17 protein *in vitro* or *in vivo*.[83] Taken together, most published evidence favors the idea that, in the airways, IL-17 protein is not released during physiological conditions.[78,84]

The receptor for IL-17

The human receptor for IL-17 displays a unique structure; it is a type I membrane protein containing a 293 amino acid extracellular domain, a 21 amino acid transmembrane domain and a 525 amino acid cytoplasmic tail.[78,79,85–87] The mRNA for the human IL-17 receptor is expressed in a wide range of cells, including airway epithelial cells, foreskin and synovial fibroblasts, B and T lymphocytes and myelomonocytic cells.[85–87] In line with this, the mRNA for the rodent IL-17A receptor is present in rodent lungs, kidneys, liver and spleen.[85,86] Rodent cells such as fibroblasts, intestinal epithelial cells and various T lymphocyte clones also express mRNA for the rodent IL-17A receptor.[85,86] Of note, the IL-17 receptor protein appears to be expressed constitutively in several of these human and rodent cells, indicating a general 'readiness' to respond to IL-17 under physiological conditions.

Neutrophil-mobilizing factors increased in airway epithelial cells by IL-17

Various human airway epithelial cells respond to stimulation with human IL-17 protein *in vitro* by producing and releasing the C-X-C chemokine IL-8.[3,88–91] The

same is true for the release of the C-X-C chemokines growth-related oncogene (GRO)-α and granulocyte chemotactic protein (GCP)-2.[91,92] In the case of IL-8 and GRO-α, this chemokine production is probably specific because it is attenuated if the human IL-17 protein is coincubated with an antihuman IL-17 antibody.[3,92] In terms of gene expression, as well as protein release, human IL-17 protein increases IL-8 and GRO-α to a similar degree as does TNF-α.[92] Interestingly, there are functional data showing that conditioned cell medium from human airway epithelial cells stimulated with human IL-17 protein does cause neutrophil chemotaxis *in vitro*.[3] It appears as if the major part of this effect is mediated via IL-8, because preincubation of the conditioned medium with an antihuman IL-8 antibody attenuates the chemotactic activity of the cell medium and human IL-17 protein *per se* does not cause chemotaxis for human blood neutrophils *in vitro*.

Treatment with a glucocorticoid (hydrocortisone) attenuates the induced release of C-X-C chemokines, such as IL-8, GRO-α and GCP-2, caused by human IL-17 protein in human airway epithelial cells *in vitro*.[3,89,91] However, there are conflicting data suggesting that the IL-17-induced IL-8 release in human airway epithelial cells, as opposed to TNF-α-induced IL-8 release, is resistant to a glucocorticoid (dexamethasone) under certain conditions.[92] The basis for this discrepancy remains unclear, but it may relate to the fact that, in the specific study mentioned, epithelial cells were cultured in the presence of a glucocorticoid prior to the re-addition of a glucocorticoid.

Interestingly, it appears as if IL-17-induced release of IL-8, but not of GCP-2 or GRO-α, is potentiated by the β_2-adrenergic receptor agonist salbutamol in human bronchial epithelial cells *in vitro*.[91] Thus, this observation is compatible with a selective and potentially proinflammatory effect on neutrophil recruitment being caused by a β_2-adrenergic receptor agonist, but it remains to be confirmed whether this is the basis for a corresponding effect in airways *in vivo*.[57,93–95]

It is not yet certain whether the IL-17-induced release of IL-8 and other C-X-C chemokines in human airway epithelial cells involves a nuclear factor (NF)-κB-inducing kinase, as it does in intestinal epithelial cells *in vitro*.[96] However, it seems likely that it does, because NF-κB is involved in initiating the transcription of IL-8 in response to a variety of stimuli other than IL-17 in airway epithelial cells, including oxygen free radicals, bacterial products and particulate matter.[97–101] The role of mitogen-activated protein kinases (MAPK) is more certain; several studies have indicated that these kinases are involved in mediating the intracellular response to IL-17, a response that subsequently leads to the release of C-X-C chemokines in human airway epithelial cells.[89,91,92] Thus, an inhibitor of the MAPK p38 attenuates IL-17-induced release of IL-8 and the same is true for an inhibitor of the MAPK extracellular signal-regulated kinase (ERK) in transformed human airway epithelial cells *in vitro*, even though only the involvement of ERK has been confirmed in primary human airway epithelial cells *in vitro*.[89,90]

It is also interesting that IL-17 is capable of interacting with other proinflammatory cytokines when causing the release of C-X-C chemokines. Thus, costimulation of human airway epithelial cells with the Th1 cytokine TNF-α substantially augments the release of C-X-C chemokines, such as IL-8 and GRO-α, compared with stimulation with IL-17 alone.[3,92] Similarly, costimulation of human airway epithelial cells with the Th1 cytokine interferon (IFN)-γ augments the IL-17-induced release of IL-8 in human airway epithelial cells.[90] Costimulation with the Th2 cytokines IL-4 or IL-13 also augments IL-17-induced IL-8 release in these cells.[90]

Human airway epithelial cells also respond to stimulation with human IL-17 by releasing the potentially neutrophil-activating cytokine IL-6 *in vitro*.[85,88–90,92] Just as for IL-8, the intracellular pathways appear to involve MAPK, even though there are conflicting data on the involvement of the particular MAPK p38, whereas the involvement of ERK has been confirmed in transformed and primary human airway epithelial cells.[88,89] Again, costimulation with the Th1 cytokine IFN-γ augments the release of IL-6.[90] It remains unknown whether this type of IL-6 release is sensitive to a glucocorticoid or a β_2-adrenergic receptor agonist.

There is also evidence that IL-17 can stimulate the release of growth factors in human airway epithelial cells under certain conditions.[92,102] In these epithelial cells, IL-17 releases granulocyte colony stimulating factor (G-CSF) as well as GM-CSF *in vitro* and the effects of IL-17 on the release of G-CSF and GM-CSF proteins are of a similar order of magnitude as seen with TNF-α.[92,102] Similarly, in terms of gene expression, IL-17 increases G-CSF to a similar degree as does TNF-α.[92] In the case of the release of G-CSF protein, costimulation with TNF-α causes a truly synergistic effect compared with stimulation with IL-17 alone[92] in human airway epithelial cells. This seems to be true for GM-CSF also.[102] Furthermore, there

are data suggesting that the effect of IL-17 on GM-CSF protein is functionally relevant in terms of increasing the survival of human neutrophils, at least *in vitro*.[102]

Compared with TNF-α, stimulation with IL-17 alone does not cause any substantial increase in expression of the gene or mRNA for intracellular adhesion molecule (ICAM)-1 in human airway epithelial cells *in vitro*.[90] Nor does IL-17 increase ICAM-1 protein in these cells.[90] However, costimulation of human airway epithelial cells with human IL-17 plus the Th1 cytokine IFN-γ does cause a marked increase in ICAM-1 protein and the same is true for costimulation with the Th2 cytokines IL-4 and IL-13.[90] At present, there is no published functional evaluation of these *in vitro* data on ICAM-1.

Neutrophil-mobilizing factors increased in non-epithelial cells by IL-17

It is now clear that IL-17 can increase neutrophil-mobilizing factors in several non-epithelial stromal cells of potential relevance for inflammation in the airways and lungs. Thus, human venous endothelial cells, cells that constitute a crucial barrier for the extravasation of neutrophils, respond to human IL-17 by releasing IL-8 *in vitro* and this release is sensitive to a glucuorticoid (hydrocortisone).[3] Primary human lung fibroblasts, cells that possess the potential to communicate with the neutrophil locally in lung tissue, also respond to stimulation with human IL-17 by producing and releasing IL-6 and IL-8 *in vitro* and the same is true for IL-6 release in embryonic lung fibroblasts.[83] Again, this response to IL-17 appears to be sensitive to a glucocorticoid (dexamethasone).[83] Interestingly, there is now also a preliminary report indicating that human IL-17 stimulates primary human airway smooth muscle cells to release IL-8 *in vitro and* that this response is not sensitive to a glucccorticoid.[103] At present, there are no studies evaluating the functional significance of these *in vitro* findings in terms of neutrophil recruitment or activation.

Accumulation of neutrophils in the airways and lungs caused by IL-17 *in vivo*

Several *in vivo* studies on rodents have shown that local administration of IL-17 protein from humans and rodents causes a substantial accumulation of neutrophils in the airways.[3,80,102,104,105] This *in vivo* response to IL-17 seems to be protein specific, because pretreatment of the IL-17 protein with a neutralizing anti-human IL-17 antibody attenuates its effect.[3] In rodent airways, the effect of IL-17 on neutrophil accumulation is as selective as that of the Th1 cytokine IL-1β.[104] One study indicates that systemic pretreatment with a glucocorticoid (dexamethasone) attenuates the effect of IL-17 on neutrophil accumulation.[3]

It has been shown previously that the concentration of the rodent C-X-C chemokine macrophage inflammatory protein (MIP)-2 is increased in the airways after stimulation with IL-17 protein *in vivo*.[3] In line with this, a neutralizing anti-MIP-2 antibody does attenuate the IL-17-induced accumulation of neutrophils in the airways.[3] There is now also evidence that the IL-17-induced release of IL-6 plays a role similar to that of MIP-2 in the accumulation of neutrophils in rodent airways.[80] In addition, GM-CSF plays a role for the accumulation of neutrophils caused by IL-17 and TNF-α in rodent airways *in vivo*.[102] It also appears as if endogenous tachykinins, modulated by neutral endopeptidase and acting on NK_1 receptors, facilitate the IL-17-induced accumulation of neutrophils in rodent airways *in vivo*.[104]

There is evidence that IL-17 can activate accumulated neutrophils in the airways *in vivo*.[105] This effect may be mediated mainly through indirect mechanisms, because local administration of IL-17 protein causes an increase in elastase and myeloperoxidase (MPO) activity in rodent airways *in vivo*, but no corresponding effect is observed when isolated blood neutrophils from rodents are stimulated by IL-17 protein *in vitro*.[105] In contrast with IL-17, local administration of IL-1β protein does not increase MPO or elastase activity, even though it does accumulate as many neutrophils in rodent airways *in vivo*.[105] Of note, although, local administration of rodent IL-1β plus human IL-17 substantially enhances the aforementioned increase in elastase activity, without causing any any pronounced additional increase in neutrophil accumulation.

Interleukin-17 in airway and lung inflammation

The evidence for a role for IL-17 in human airway and lung disease is still limited. There is one study showing a substantial increase in free soluble IL-17 protein in the airways of healthy volunteers after exposure to organic dust, in association with a dramatic, local accumulation of neutrophils.[84] Presumably this type of airway inflammation represents the Th1 type.

There is also one study showing a modest increase in free soluble IL-17 protein in the airways of patients with

asthma, associated with an increase in immunoreactivity for intracellular IL-17 protein in airway inflammatory cells.[83] It appears feasible that this type of airway inflammation represents the Th2 type. There are no published data yet on putative neutrophil activation associated with the presence of IL-17 protein in human airways.

In addition to the data on human airways, there is now an increasing amount of data on rodent airways *in vivo*, compatible with IL-17 playing a role in the accumulation of neutrophils in airway disease. Thus, rodents lacking the receptor for IL-17 are more susceptiable to bacterial airway infection caused by *Klebsiella pneumonie* than are wild-type rodents and this is paralleled by a weakened mobilization of neutrophils in the airways.[106,107] In line with this, local administration of endotoxin from *Escherichia coli* requires the presence of endogenous IL-17 protein in order to mobilize neutrophils in the airways.[80] It is also clear that local administration of this endotoxin increases the concentration of IL-17 protein in rodent airways *in vivo*, compatible with data from another study showing that endotoxin from *E. coli* increases the mRNA for IL-17 in rodent airways.[80,108] Indeed, all these findings are compatible with IL-17 being involved in airway inflammation of the Th1 type.

Interestingly, two recent studies on rodents *in vivo* lend further support to an involvement of IL-17 protein in airway inflammation of the Th2 type. One of these studies demonstrates that allergen challenge increases the mRNA for IL-17 in sensitized airways.[109] This study also indicates that endogenous IL-17 protein is required for allergen-induced accumulation of neutrophils and that endogenous IL-17 actually suppresses the local production of IL-5. Finally, a second study suggests that endogenous IL-17 is involved in mediating allergen-induced bronchial hyperreactivity because sensitized rodents lacking the gene for endogenous IL-17 protein display less reactivity to metacholine after allergen challenge than sensitized wild-type rodents.[110]

Future research on IL-17

In conclusion, there is substantial evidence that an exaggerated accumulation and activation of neutrophils is linked to the course of obstructive airway disease in humans. There is also evidence of plausible pathogenetic mechanisms involving the neutrophil in acute, severe asthma and COPD. The cytokine IL-17 now emerges as a candidate mediator for a link between the activation of certain T lymphocytes and the accumulation and subsequent activation of neutrophils in airway and lung disease, even though its specific role in obstructive airway disease remains to be determined. Interleukin-17 appears to exert its neutrophil-orchestrating activity indirectly, through stimulation of a number of local cells in the airways and lungs, resulting in the subsequent production and release of a variety of cytokines directly affecting neutrophils. For these reasons, it appears important to document the presence and concentrations of IL-17 in patients with various degrees of obstructive airway disease, in clinically stable patients and in patients with acute exacerbations. Data from these type of studies may reveal whether targeting IL-17 is a plausible strategy for the development of novel pharmacotherapeutic interventions against obstructive airway disease.

Acknowledgments

This work was supported the Swedish Heart–Lung Fund, the Swedish Research Council (K2002–74X-09048-13A), the Vårdal Foundation and Åke Wiberg's Foundation. No support, direct or indirect, was obtained from the tobacco industry.

References

1 Rouvier E, Luciani MF, Mattei MG, Denizof F, Golstein P. CTLA-8, cloned from an activated T cell, bearing AU-rich messenger RNA instability sequences, and homologous to a herpes virus saimiri gene. *J. Immunol.* 1993; **150**: 5445–56.

2 Yao Z, Painter SL, Fanslow WC *et al.* Human IL-17: A novel cytokine derived from T cells. *J. Immunol.* 1995; **155**: 5483–6.

3 Laan M, Cui ZH, Hoshino H *et al.* Neutrophil recruitment by human IL-17 via C-X-C chemokine release in the airways. *J. Immunol.* 1999; **162**: 2347–52.

4 Fahy JV, Kim KW, Kim J, Liu J, Boushey HA. Prominent neutrophilic inflammation in sputum from subjects with asthma excacerbation. *J. Allergy Clin. Immunol.* 1995; **95**: 843–52.

5 Ordonez CL, Shaughnessy TE, Matthay MA, Fahy JV. Increased neutrophil numbers and IL-8 levels in airway secretions in acute severe asthma. Clinical and biological significance. *Am. J. Respir. Crit. Care Med.* 2000; **161**: 1185–60.

6 Vignola AM, Bonanno A, Mirabella A *et al.* Increased level of elastase and alpha 1-antitrypsin in sputum of asthmatic patients. *Am. J. Respir. Crit. Care Med.* 1998; **157**: 505–11.

7 Lamblin C, Gosset P, Tillie-Leblond I *et al.* Bronchial neutrophilia in patients with noninfectious status asthmaticus. *Am. J. Respir. Crit. Care Med.* 1998; **157**: 394–402.

8 Jatakanon A, Uasuf C, Maziak W, Lim S, Chung KF, Barnes PJ. Neutrophilic inflammation in severe persitent asthma. *Am. J. Respir. Crit. Care Med.* 1999; **160**: 1532–9.

9 Wenzel SE, Schwartz LB, Langmack EL *et al.* Evidence that severe asthma can be divided into two inflammatory subtypes with distinct physiologic and clinical characteristics. *Am. J. Respir. Crit. Care Med.* 1999; **160**: 1001–8.

10 Saetta M, Turato G, Facchini F *et al.* Inflammatory cells in the bronchial glands of smokers with chronic bronchitis. *Am. J. Respir. Crit. Care Med.* 1997; **156**: 1633–9.

11 Riise GC, Ahlstedt S, Larsson S *et al.* Bronchial inflammation in chronic bronchitis assessed by measurement of cell products in bronchial lavage fluid. *Thorax* 1995; **50**: 360–5.

12 Balbi B, Bason C, Balleari E *et al.* Increased bronchoalveolar granulocytes and granulocyte/colony-stimulating factor during exacerbations of chronic bronchitis. *Eur. Respir. J.* 1997; **10**: 846–50.

13 Betsuyaku T, Nishimura M, Takeyabu K *et al.* Neutrophil granule proteins in bronchoalveolar lavage fluid from subjects with subclinical emphysema. *Am. J. Respir. Crit. Care Med.* 1999; **159**: 1985–91.

14 Aaron SD, Angel JB, Lunau M *et al.* Granulocyte inflammatory markers and airway infection during acute exacerbation of chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 2001; **163**: 349–55.

15 Balzano G, Stefanelli F, Irorio C *et al.* Eosinophilic inflammation in stable chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 1999; **160**: 1486–92.

16 Di Stefano A, Capelli A, Lusardi M *et al.* Severity of airflow limitation is associated with severity of airway inflammation in smokers. *Am. J. Respir. Crit. Care Med.* 1999; **158**: 1277–85.

17 Soler N, Ewig S, Torres A, Filella X, Gonzales J, Zaubet A. Airway inflammation and bronchial microbial patterns in patients with stable chronic obstructive pulmonary disease. *Eur. Respir. J.* 1999; **14**: 1015–22.

18 Noguera A, Batle S, Miralles C *et al.* Enhanced neutrophil response in chronic obstructive pulmonary disease. *Thorax* 2001; **56**: 432–7.

19 Betz R, Kohlhaufl M, Kassner G *et al.* Increased sputum IL-8 and IL-5 in asymptomatic non-specific hyperresponsiveness. *Lung* 2001; **179**: 119–33.

20 Stanescu D, Sanna A, Kostianev S, Calgagni PG, Fabbri LM, Maestrelli P. Airway obstruction, chronic expectoration, and rapid decline in FEV_1 in smokers are associated with increased levels of sputum neutrophils. *Thorax* 1996; **51**: 267–71.

21 Fujimura M, Xiu Q, Tsujiura M *et al.* Role of leukotriene B_4 in bronchial hyperresponsiveness induced by interleukin-8. *Eur. Respir. J.* 1998; **11**: 306–11.

22 Matsumoto K, Aizawa H, Inoue H, Koto H, Nakano H, Hara N. Role of neutrophil elastase in ozone-induced airway responses in guinea-pigs. *Eur. Respir. J.* 1999; **14**: 1088–94.

23 Suzuki T, Wang W, Lin JT, Shirato K, Mitsuhashi H, Inoue H. Aerosolised human neutrophil elastase induces airway constriction and hyper-responsiveness with protection by intravenous pretreatment with half-length secretory leukoprotease inhibitor. *Am. J. Respir. Crit. Care Med.* 1996; **153**: 1405–11.

24 Chen XJ, Hedlund LW, Moller HE, Chawla MS, Maronpot RR. Detection of emphysema in rat lungs by using magnetic resonance measurements of ^3He diffusion. *Proc. Natl Acad. Sci. USA* 2000; **10**: 11 478–81.

25 Zhu YK, Liu XD, Skold CM *et al.* Synergistic neutrophil elastase–cytokine interaction degrades collagen in three dimensional culture. *Am. J. Physiol. Lung Cell. Mol. Physiol.* 2000; **281**: L868–78.

26 Sampson AP. The role of eosinophils and neutrophils in inflammation. *Clin. Exp. Allergy* 2000; **30**: 22–7.

27 Schuster A, Ueki I, Nadel JA. Neutrophil elastase stimulates tracheal submucosal gland secretion that is inhibited by ICI 200,355. *Am. J Physiol.* 1992; **262**: L86–91.

28 Nadel JA, Takeyama K, Augusti C. Role of neutrophil elastase in hypersecretion in asthma. *Eur. Respir. J.* 1999; **13**: 190–6.

29 Culpitt AV, Maziak W, Loukidis S, Nightingale JA, Matthews JL, Barnes PJ. Effect of high dose inhaled steroid on cells, cytokines and proteases in induced sputum in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 1999; **160**: 1635–9.

30 Prikk K, Maisis P, Pirila E *et al.* Airway obstruction correlates with collagenase-2 (MMP-8) expression and activation in bronchial asthma. *Lab. Invest.* 2002; **82**: 1534–45.

31 Cataldo DD, Bettiol J, Noel A, Bartsch P, Foidart JM, Lous R. Matrix metalloproteinase-9, but not tissue inhibitor of matrix metalloproteinase-1, increases in the sputum from allergic asthmatic patients after allergen challenge. *Chest* 2002; **122**: 1553–9.

32 Mattos W, Lim S, Russel R, Jatakanon A, Chung KF, Barnes PJ. Matric metalloproteinase-9 expression in asthma: Effect of asthma severity, allergen challenge, and inhaled glucocorticoids. *Chest* 2002; **122**: 1543–52.

33 Lee YC, Lee HB, Rhee YK, Song CH. The involvement of matrix metalloproteinase-9 in airway inflammation of patients with acute asthma. *Clin. Exp. Allergy* 2001; **31**: 1623–30.

34 Cataldo D, Munuat C, Noel A *et al.* MMP-2- and MMP-9-linked gelatinolytic activity in the sputum from patients with asthma and chronic obstructive pulmonary disease. *Int. Arch. Allergy Immunol.* 2000; **123**: 259–67.

35 Cataldo DD, Tournoy KG, Vermaelen K *et al.* Matrix metalloproteinase-9 deficiency impairs cellular infiltration and bronchial hyperresponsiveness during allergen-induced airway inflammation. *Am. J. Pathol.* 2002; **161**: 491–8.

36 Watanabe M, Kaihatsu T, Miwa M, Maeda T. Ca^{2+}/calmodulin-dependent protein kinase II inhibitors potentiate superoxide production in polymorphonuclear leukocytes. *J. Pharm. Pharmacol.* 1999; **51**: 295–300.

37 Cortijo J, Villagrasa V, Pons R *et al*. Bronchodilator and anti-inflammatory activities of glaucine: *In vitro* studies on human airway smooth muscle and polymorphonuclear leukocytes. *Br. J. Pharmacol*. 1999; **127**: 1641–51.

38 Sustiel AM, Joseph B, Rocklin RE, Borish L. Asthmatic patients have neutophils that exhibit diminished responsiveness to adenosine. *Am. Rev. Respir. Dis*. 1989; **140**: 1556–61.

39 Massion P, Lindén A, Inoue H, Mathy M, Grattan KM, Nadel JA. Dimethyl sulfoxide decreases interleukin-8-mediated neutrophil recruitment in the airways. *Am. J. Physiol*. 1996; **271**: L838–43.

40 Inoue H, Aizawa H, Nakano H *et al*. Nitric oxide synthase inhibitors attenuate ozone-induced airway inflammation in guinea pigs. Possible role of interleukin-8. *Am. J. Respir. Crit. Care Med*. 2000; **161**: 249–56.

41 Stevens WH, Inman MD, Wattie J, O'Byrne PM. Allergen-induced oxygen radical release from bronchoalveolar lavage cells and airway hyperresponsiveness in dogs. *Am. J. Respir. Crit. Care Med*. 1995; **151**: 1526–31.

42 Takahashi T, Miura M, Katsumata U *et al*. Involvement of superoxide in ozone-induced airway hyperresponsiveness inanaesthetized cats. *Am. Rev. Respir. Dis*. 1993; **148**: 103–6.

43 Nakano H, Aizawa H, Matsumoto K, Fukuyama S, Inoue H, Hara N. Cyclooxygenase-2 participates in the late phase of airway hyperresponsiveness after ozone exposure in guinea pigs. *Eur. J. Pharmacol*. 2000; **403**: 267–75.

44 Matsui S, Jones GL, Woolley MJ, Lane CC, Gontovnick LS, O'Byrne PM. The effect of antioxidants on ozone-induced airway hyperresponsiveness in dogs. *Am. Rev. Respir. Dis*. 1991; **144**: 1287–90.

45 Hallahan AR, Armour CL, Black JL. Products of neutrophils and eosinophils increase the responsiveness of human isolated bronchial tissue. *Eur. Respir. J*. 1990; **3**: 554–8.

46 Zeng L, Shum H, Tipoe GL *et al*. Macrophages, neutrophils and tumor necrosis factor-alpha expression in bronchiectatic airways *in vivo*. *Respir. Med*. 2001; **95**: 792–8.

47 Volcano M, Alves Rosa MF, Minnucci FS, Chernavsky AC, Isturiz MA. *N*-Formyl-methionyl-leucyl-phenylalanine (fMLP) inhibits tumor necrosis factor-alpha (TNF-alpha) production in lipopolysaccharide (LPS)-stimulated human neutrophils. *Clin. Exp. Immunol*. 1998; **113**: 39–47.

48 Page SM, Gleich GJ, Roebuck KA, Thomas LL. Stimulation of neutrophil interleukin-8 production by eosinophil granule major basic protein. *Am. J. Respir. Cell. Mol. Biol*. 1999; **21**: 230–7.

49 Keatings VM, Collins PD, Scott DM, Barnes PJ. Differences in interleukin-8 and tumor necrosis factor-alpha in induced sputum from patients with chronic obstructive pulmonary disease or asthma. *Am. J. Respir. Crit. Care Med*. 1996; **153**: 530–4.

50 Sibelius U, Hattar K, Hoffman S *et al*. Distinct pathways of lipopolysaccharide priming of human neutrophil respiratory burst: Role of lipid mediator synthesis and sensitivity to interleukin-10. *Crit. Care Med*. 2002; **30**: 2306–12.

51 Gambero A, Landucci EC, Toyama MH *et al*. Human neutrophil migration *in vitro* induced by secretory phospholipases A_2: A role for cell surface glycosaminoglycans. *Biochem. Pharmacol*. 2002; **63**: 65–72.

52 Falt J, Dahlgren C, Ridell M. Difference in neutrophil cytokine production induced by pathogenic and non-pathogenic mycobacteria. *APMIS* 2002; **110**: 593–600.

53 Kuhns DB, Nelson EL, Alvord WG, Gallin JI. Fibrinogen induces IL-8 synthesis in human neutrophils stimulated with formyl-methionyl-leucyl-phenulalanine or leukotriene B_4. *J. Immunol*. 2001; **167**: 2869–78.

54 Koller M, Wick M, Muhr G. Decreased leukotriene release from neutrophils after severe trauma: Role of immature cells. *Inflammation* 2001; **25**: 53–9.

55 Xiu Q, Fujimura M, Nomura M *et al*. Bronchial hyperresponsiveness and airway neutrophil accumulation induced by interleukin-8 and the effect of the thromboxane A_2 antagonist S-1452 in guinea-pigs. *Clin. Exp. Allergy* 1995; **25**: 51–9.

56 Hessel EM, Van Oosterhout AJ, Van Ark I *et al*. Development of airway hyperresponsiveness is dependent on interferon-gamma and independent of eosinophil infiltration. *Am. J. Respir. Crit. Care Med*. 1997; **160**: 325–34.

57 Lindén A. Increased interleukin-8 release by beta-adrenoceptor activation in human transformed bronchial epithelial cells. *Br. J. Pharmacol*. 1996; **119**: 402–6.

58 Jorens PG, Richman-Eisenstadt JBY, Housset BP *et al*. Interleukin-8 induces neutrophil accumulation but not protease secretion in the canine trachea. *Am. J Physiol*. 1992; **263**: L708–13.

59 Amin K, Ludviksdottir D, Janson C *et al*. Inflammation and structural changes in the airways of patients with atopic and non-atopic asthma. *Am. J. Respir. Crit. Care Med*. 2000; **162**: 2295–301.

60 Mazarella G, Grella E, D'Auria D *et al*. Phenotypic features of alveolar monocytes/macrophages and IL-8 gene activation by IL-1 and TNF-alpha in asthmatic patients. *Allergy* 2000; **55**: 36–41.

61 Marini M, Vittori E, Hollemborg J, Mattoli S. Expression of the potent inflammatory cytokines, granulocyte–macrophage-colony-stimulation factor and interleukin-6 and interleukin-8, in bronchial epithelial cells of patients with asthma. *J. Allergy Clin. Immunol*. 1992; **89**: 1001–9.

62 Yousefi S, Hemmann S, Weber M *et al*. IL-8 is expressed by human peripheral blood eosinophils: Evidence for increased secretion in asthma. *J. Immunol*. 1995; **154**: 5481–90.

63 Hoshi H, Ohno M, Hinma M *et al*. IL-5, IL-8 and GM-CSF immunostaining of sputum cells in bronchial asthma and chronic bronchitis. *Clin. Exp. Allergy* 1995; **25**: 720–8.

64 Laitinen LA, Laitinen A, Haahtela T. Airway mucosal inflammation even in patients with newly diagnosed asthma. *Am. Rev. Respir. Dis*. 1993; **147**: 697–704.

65 Gavett SH, Chen X, Finkelman F, Wills-Karp M. Depletion of murine $CD4^+$ T lymphocytes prevents antigen-induced airway hyperreactivity and pulmonary eosinophilia. *Am. J. Respir. Cell Mol. Biol*. 1994; **10**: 587–93.

66 Renzi PM, Yang JP, Diamantstein T, Martin JG. Effects of depletion of cells bearing the interleukin-2 receptor on immunoglobulin production and allergic airway responses in the rat. *Am. J. Respir. Crit. Care Med.* 1996; **153**: 1214–21.
67 Rutgers SR, Postma DS, ten Hacken NH *et al.* Ongoing airway inflammation in patients with COPD who do not currently smoke. *Thorax* 2000; **55**: 12–18.
68 Turato G, Zuin R, Monti S *et al.* Airway inflammation in severe chronic obstructive pulmonary disease. Relationship with lung function and radiologic emphysema. *Am. J. Respir. Crit. Care Med.* 2002; **166**: 105–10.
69 Meshi B, Vitalis TZ, Ionescu D *et al.* Emphysemateous lung destruction by cigarette smoke. The effects of latent adenoviral infection on the lung inflammatory response. *Am. J. Respir. Cell Mol. Biol.* 2002; **26**: 52–7.
70 Walker C, Kaegi MK, Braun P, Blaser K. Activated T cells and eosinophilia in bronchoalveolar lavages from subjects with asthma correlated with disease severity. *J. Allergy Clin. Immunol.* 1991; **88**: 935–42.
71 Mishima H, Hojo M, Watanabe A, Hamid QA, Martin JG. $CD4^+$ T cells can induce airway hyperresponsiveness to allergen challenge in the brown Norway rat. *Am. J. Respir. Crit. Care Med.* 1998; **158**: 1863–70.
72 De Sanctis GT, Itoh A, Green FHY *et al.* T-Lymphocytes regulate genetically determined airway hyperresponsiveness in mice. *Nat. Med.* 1997; **4**: 460–2.
73 Nakajima H, Iwamoto I, Tomoe S *et al.* $CD4^+$ T-lymphocytes and interleukin-5 mediate antigen-induced eosinophil infiltration into the mouse trachea. *Am. Rev. Respir. Dis.* 1992; **146**: 374–7.
74 Cieslewics G, Tomkinson A, Adler A *et al.* The late, but not early, asthmatic response is dependent on IL-5 and correlates with eosinophil infiltrarion. *J. Clin. Invest.* 1999; **104**: 301–8.
75 Tillie-Leblond I, Hammad H, Desurmont S *et al.* CC chemokines and interleukin-5 in bronchial lavage fluid from patients with status asthmaticus. Potential implications in eosinophil recruitment. *Am. J. Respir. Crit. Care Med.* 2000; **162**: 586–92.
76 Leckie MJ, ten Brink A, Khan J *et al.* Effects of an interleukin-5 blocking monoclonal antibody on eosinophils. *Lancet* 2000; **356**: 2114–16.
77 Tomaki M, Zhao LL, Sjöstrand M, Lindén A, Ichinose M, Lötvall J. Comparison of effects of anti-IL-3, IL-5 and GM-CSF treatments on eosinophilopoesis and airway eosinophilia induced by allergen. *Pulmon. Pharmacol. Ther.* 2002; **15**: 161–8.
78 Fossiez F, Banchereau J, Murray R, Van Kooten C, Garrone P, Lebecque S. Interleukin-17. *Intern. Rev. Immunol.* 1998; **16**: 541–51.
79 Spriggs MK. Interleukin-17 and its receptor. *J. Clin. Immunol.* 1997; **17**: 366–9.
80 Miyamoto M, Prause O, Laan M, Sjöstrand M, Lötvall J, Lindén A. Endogenous IL-17 mediates endotoxin-induced airway neutrophilia in mice *in vivo*. *J. Immunol.* 2003; **170**: 4665–72.
81 Shin H, Benbernou N, Esnault S, Guenounou M. Expression of IL-17 in human memory CD45RO+ T lymphocytes and its regulation by protein kinase A pathway. *Cytokine* 1999; **11**: 257–66.
82 Aarvak T, Chabaud M, Miossec P, Natvig JB. IL-17 is produced by some proinflammatory Th_1/Th_0 cells but not Th_2 cells. *J. Immunol.* 1999; **162**: 1246–51.
83 Molet S, Hamid QA, Davoine F *et al.* Interleukin-17 is increased in asthmatic airways and induces human fibroblasts to produce cytokines. *J. Allergy Clin. Immunol.* 2001; **108**: 103–9.
84 Laan M, Palmberg L, Larsson K, Linden A. Free, soluble interleukin-17 protein during severe inflammation in human airways. *Eur. Respir. J.* 2002; **19**: 534–7.
85 Yao Z, Spriggs M, Derry J *et al.* Molecular characterisation of the human interleukin (IL)-17 receptor. *Cytokine* 1997; **9**: 794–800.
86 Yao Z, Fanslow FC, Seldin MF *et al.* Herpesvirus Saimiri encodes a new cytokine, IL-17, which binds to a novel cytokine receptor. *Immunity* 1995; **3**: 811–21.
87 Kehlen A, Thiele K, Rieman D, Langner J. Expression, modulation and signalling of IL-17 recepor in fibroblast-like synoviocytes of patients with rheumatoid arthritis. *Clin. Exp. Immunol.* 2002; **127**: 539–46.
88 Fossiez F, Djossou O, Chomarat P *et al.* T cell interleukin-17 induces stromal cells to produce proinflammatory and hematopoietic cytokines. *J. Exp. Med.* 1996; **183**: 2593–603.
89 Laan M, Lötvall J, Chung KF, Lindén A. IL-17-induced cytokine release in human bronchial epithelial cells *in vitro*: Role of mitogen-activated protein (MAP) kinases. *Br. J. Pharmacol.* 2001; **133**: 200–6.
90 Kawaguchi M, Kokubu F, Kuga H *et al.* Modulation of bronchial epithelial cells by IL-17. *J. Allergy Clin. Immunol.* 2001; **108**: 804–9.
91 Prause O, Laan M, Lotvall J, Lindén A. Pharmacological modulation of interleukin-17-induced GCP-2-, GRO-α- and interleukin-8 release in human bronchial epithelial cells. *Eur. J. Pharmacol.* 2003; **462**: 193–8.
92 Jones CE, Chan K. Interleukin-17 stimulates the expression of interleukin-8, growth-related oncogene-α, and granulocyte-colony-stimulating factor by human airway epithelial cells. *Am. J. Respir. Cell Mol. Biol.* 2002; **26**: 748–53.
93 Cockroft DW, MacParland CP, Britto SA, Swystun VA, Rutherford BC. Regular inhaled salbutamol and airway responsiveness to allergen. *Lancet* 1993; **342**: 833–7.
94 Cockroft DW, O'Byrne P, Swystun VA, Baghat R Regular use of inhaled salbutamol and the allergen-induced late asthmatic response. *J. Allergy Clin. Immunol.* 1995; **96**: 44–9.
95 Kamachi A, Munakata M, Nasuhara Y *et al.* Enhancement of goblet cell hyperplasia and airway hyperresponsiveness by salbutamol in a rat model of atopic asthma. *Thorax* 2001; **56**: 19–24.
96 Awane M, Andres PG, Li DJ, Reinecker HC. NF-κB-inducing kinase is a common mediator of IL-17-, TNF-α-, and IL-1β-induced chemokine promoter activation in intestinal epithelial cells. *J. Immunol.* 1999; **162**: 5337–44.

97 Mori N, Oishi K, Sar B *et al*. Essential role of transcription factor nuclear factor-kappa B in regulation of interleukin-8 gene expression by nitrite reductase from *Pseudomonas aeruginosa* in respiratory epithelial cells. *Infect. Immun.* 1999; **67**: 3872–8.
98 Harper R, Wu K, Chang MM *et al*. Activation of nuclear factor-kappa B in airway epithelial cells by thioredoxin but not *N*-acetylcysteine and glutathione. *Am. J. Respir. Cell Mol. Biol.* 2001; **25**: 178–85.
99 Chang MM, Harper R, Hyde DM, Wu R. A novel mechanism of retinoic acid-enhanced interleukin-8 gene expression in airway epithelium. *Am. J. Respir. Cell Mol. Biol.* 2000; **22**: 502–10.
100 Kennedy T, Ghio AJ, Reed W *et al*. Copper-dependent inflammation and nuclear factor-kappa B activation by particulate air pollution. *Am. J. Respir. Cell Mol. Biol.* 1998; **19**: 366–78.
101 Mastronarde JG, Monick MM, Mukaida N, Matsushima K, Hunninghake GW. Activator protein-1 is the preferred transcription factor for cooperative interaction with nuclear factor-kappa B in respiratory syncytial virus-induced interleukin-8 gene expression in airway epithelium. *J. Infect. Dis.* 1998; **177**: 1275–81.
102 Laan M, Prause O, Miyamoto M *et al*. A role of GM-CSF in the accumulation of neutrophils in the airways caused by IL-17 and TNF-alpha. *Eur. Respir. J.* 2003; **21**: 1–7.
103 Vanaudenaerde BM, Wuyts WA, Dupont LJ, Demetdts MG, Raemdonck DV, Verleden GM. The possible role of human airway smooth muscle cells (HASMC) in the pathogenesis of obliterative bronchiolitis after lung transplantation. *Eur. Respir. J.* 2002; **20** (Suppl. 38): S348 (Abstract).
104 Hoshino H, Lötvall J, Skoogh BE, Lindén A. Neutrophil recruitment by IL-17 into rat airways *in vivo*: Role of tachykinins. *Am. J. Respir. Crit. Care Med.* 1999; **159**: 1423–8.
105 Hoshino H, Laan M, Sjöstrand M, Lötvall J, Skoogh BE, Lindén A. Increased elastase and myeloperoxidase activity associated with neutrophil recruitment by IL-17 in airways *in vivo*. *J. Allergy Clin. Immunol.* 2000; **105**: 143–9.
106 Ye P, Rodriguez FH, Kanaly S *et al*. Requirement of interleukin 17 receptor signaling for lung CXC chemokine and granulocyte colony-stimulating factor expression, neutrophil recruitment, and host defense. *J. Exp. Med.* 2001; **194**: 519–27.
107 Ye P, Garvey PB, Zhang P, Nelson S, Bagby G, Summer WR, Schwarzenberger P, Shellito JE, Kolls JK. Interleukin-17 and lung host defense against *Klebisella pneumonie* infection. *Am. J. Respir. Crit. Care Med.* 2001; **25**: 335–40.
108 Larsson R, Rocksén D, Lillienhook B, Jonsson A, Bucht A. Dose-dependent activation of lymphocytes in endotoxin-induced airway inflammation. *Infect. Immun.* 2000; **68**: 6962–9.
109 Hellings PW, Kasran A, Liu Z *et al*. Interleukin-17 orchestrates the granulocyte influx into airways after allergen inhalation in a mouse model of allergic asthma. *Am. J. Respir. Crit. Care Med.* 2003; **28**: 42–50.
110 Nakae S, Komiyama Y, Nambu A *et al*. Antigen-specific T cell sensitization is impaired in IL-17-deficient mice, causing suppression of allergic cellular and humoral responses. *Immunity* 2002; **17**: 375–87.