In vitro study of regulation of IL-6 production in bronchiectasis

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Summary Persistent airway inflammation is an important pathogenetic factor in bronchiectasis, and interleukin (IL)-6 is among the mediators implicated in regulation of inflammation in bronchiectatic airways. We postulated that airway secretion with its constituents of cytokines and enzymes would provide an environment for perpetuation of inflammation in vivo. We aimed to determine the action of sputum from patients with bronchiectasis on IL-6 production from cultured normal human bronchial epithelial (NHBE) cells and its modulation by anti-inflammatory drugs in vitro.

Cultures of NHBE cells were tested with (i) sputum of bronchiectatic patients, (ii) anti-tumor necrosis factor-alpha (TNF-\textsubscript{\alpha}) pre-treated sputum, or (iii) recombinant human (rh)-TNF-\textsubscript{\alpha}. Alternatively, NHBE cells were incubated with one of the anti-inflammatory drugs before treatment with sputum or rh-TNF-\textsubscript{\alpha}. IL-6 produced into the medium was assayed by ELISA.

Sputum in bronchiectasis stimulated IL-6 production from NHBE cells by 1.9 times. This was largely attributable to TNF-\textsubscript{\alpha} as pre-incubation of sputum sol with anti-TNF-\textsubscript{\alpha} almost neutralized the sputum effect. Apart from dexamethasone, the other drugs exerted inhibitory effects on IL-6 production. Ibuprofen suppressed sputum-stimulated IL-6 production to levels above control and effect levelled off at 50–100 \(\mu\text{g/ml}\), contrasting the dose-dependent suppression to control level with MK-663 (0.1–10 \(\mu\text{g/ml}\)) and to sub-control levels with triptolide (20–1000 ng/ml).

Our results support that sputum in bronchiectasis can stimulate IL-6 production from NHBE cells, and TNF-\textsubscript{\alpha} is an important cytokine mediating the process. The suppressive effects observed with ibuprofen, triptolide and MK-663 warrant further study.

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Introduction

Bronchiectasis, the permanent dilatation of one or more bronchi, is a common respiratory condition which occurs in the west in cystic fibrosis, and in the east as sequelae of respiratory infections or as etiologically idiopathic cases. The pathogenetic mechanisms in bronchiectasis are multi-faceted including enzymatic, inflammatory, and infective elements. Sputum in bronchiectatic subjects has been shown to contain various inflammatory cytokines and elastase, which correlated with disease activity. In recent decades, major advances exploring the inflammatory network in various inflammatory airway diseases like asthma have broadened our understanding of the pathogenesis with potential therapeutic implications.

The respiratory epithelium has long been regarded as an inert barrier lining the human airway. However, there has been abundant evidence suggesting that the respiratory epithelium plays a metabolically active role in various conditions like asthma and infections. Studies on cultured human bronchial epithelial cells incubated with bacterial endotoxin demonstrated a marked increase in expression and/or release of pro-inflammatory mediators including interleukin (IL)-6, IL-8, tumor necrosis factor-alpha (TNF-α) and intercellular adhesion molecule-1 (ICAM-1). IL-6 is often used as a marker of systemic activation of pro-inflammatory cytokines.

We postulate that the vicious circle of inflammation in bronchiectasis is maintained in part by the copious bronchial secretion with its rich contents of cytokines and enzymes. Recent study has shown a significant increase in IL-6 among other cytokines in bronchoalveolar lavage fluid in subjects with bronchiectasis compared to control. This inflammatory reaction was exaggerated in subjects colonized by microorganisms with a clear relationship to the bronchial bacterial load. Similarly, sputum from subjects with non-cystic fibrosis diffuse bronchiectasis was found to have increased IL-6. In cystic fibrosis, which is mainly characterized by diffuse bronchiectasis in the lungs, plasma IL-6 levels after an exacerbation were reduced after antibiotic treatment, acting as a maker of inflammation. In this study, we explore the effect of sputum sol from subjects with bronchiectasis on the production of IL-6 from normal human bronchial epithelial (NHBE) cells and the role of sputum TNF-α in this aspect. The potential effects of four anti-inflammatory drugs on IL-6 production were also evaluated.

Materials and methods

Sample collection

Subjects with clinically and radiologically (based on high-resolution computed tomography (HRCT) scan) confirmed bronchiectasis were identified at the respiratory clinic in the Queen Mary Hospital in Hong Kong. Only those with clinical steady-state bronchiectasis were recruited. Subjects with acute infective episodes requiring antibiotics in the prior 3 weeks, and those on long-acting β2 agonists, anticholinergics, theophylline or steroids were excluded. Short-acting inhaled bronchodilator therapy was withheld in the morning of sputum collection. The quality of expectorated sputum was examined under light microscopy with presence of ≥10 buccal epithelial cells being considered salivary in origin and excluded for further experiments. Fresh sputum samples were collected in sterile pots for 4h from waking up in the morning, and ultracentrifuged at 50,000 × g for 90 min at 4°C. The supernatants (sputum sol) were separated and stored at −80°C for subsequent experiments. This study has been approved by the Ethics Committee, the University of Hong Kong.

Reagents

Lyophilized recombinant human (rh)-TNF-α (PePro Tech EC Ltd, London, UK) was reconstituted in sterilized water and aliquoted for subsequent use. Anti-human TNF-α (PePro Tech EC Ltd, London, UK) was a rabbit-derived polyclonal antibody with neutralizing activity against TNF-α which was quantitated in a cytolysis assay. Dexamethasone and ibuprofen (both from Sigma, St. Louis, MO, USA) were prepared according to the instructions from the provider. Triptolide was kindly provided by Professor DQ Yu (Chinese Academy of Medical Sciences, Beijing, China) and was isolated according to the method previously described. MK-663 (COX-2 inhibitor) was obtained from the Merck Research Laboratory.

Primary culture of human bronchial epithelial cells

One ampoule of primary NHBE cells (lot number: 8F0148, age 18, female; lot number: 8F0258, age 47, male) (Clonetics, San Diego, CA, USA) was thawed in a 37°C water bath and seeded to T-75 culture flasks containing basal medium with supplements at seeding density of 3500 cells/cm². The supplements added were 30μg/ml bovine pituitary
extract (BPE), 0.5 \mu g/ml hydrocortisone, 0.5 \mu g/ml recombinant human epidermal growth factor (hEGF), 0.5 \mu g/ml epinephrine, 10 \mu g/ml transferrin, 5 \mu g/ml insulin, 0.1 \mu g/ml retinoic acid, 6.5 \mu g/ml triiodothyronine, 50 \mu g/ml gentamicin, 50 \mu g/ml amphotericin-B and 500 \mu g/ml bovine serum albumin-fatty acid free (BSA-FAF) (Clonetics). Cells were incubated at 37 \degree C and 5% CO\textsubscript{2}. Upon 70–80% confluence, cells were recovered with trypsin/ethylenediaminetetraacetic acid (EDTA). The third generation of NHBE cells were cultured in 12-well plates coated with Collagen IV until 80% confluence for subsequent experiments. Cell viability was randomly checked to ensure no significant difference during various experiments. Specifically, Trypan Blue Exclusion Test was done on separate sets of cell cultures to ascertain that cells were viable after incubation with the highest concentration of each drug used in the study.

Assays of TNF-\alpha and IL-6

The concentration of TNF-\alpha and IL-6 in the sputum sol and supernatant of cell culture medium were measured by enzyme-linked immunoabsorbent assay (ELISA) (Amersham Pharmacia Biotech, Piscataway, NJ, USA). In brief, biotinylated antibody reagent was added to each well of a 96-well polystyrene microtitre ELISA plate coated with an antibody against the cytokine of interest. Standards and samples were then added in duplicate to the wells and incubated for 2 h at room temperature. After the incubation, each well was washed vigorously with wash buffer for three times. Streptavidin-horse reddish peroxidase was added to each well and incubated for 30 min at room temperature followed by washing three times with wash buffer. TMB substrate solution was then added into each well and incubated for another 30 min at room temperature in the dark. At the end of incubation, stop solution was added to each well of the ELISA plate. The assays were calibrated with the standard provided with the kits and optical densities were measured by a microplate reader at the wavelength of 450 nm.

Treatment of NHBE cells with sputum sol, anti-TNF-\alpha or rh-TNF-\alpha

Sputum sol samples were diluted 50-fold with basal medium, added to NHBE cells (lot 8F0148) cultured in 12-well plates and incubated at 37 \degree C and 5% CO\textsubscript{2} for 4 h. Triplicate treatments were performed for each sputum sol sample. Parallel incubations of NHBE cells in culture medium were taken as controls. After the incubations, the media were recovered and the cell-free supernatants were assayed for IL-6.

To neutralize possible effects of sputum sol TNF-\alpha on the NHBE cells, cultures in 12-well plates were incubated (4 h, 37 \degree C) with 50-fold dilutions of sol samples which had been treated (1 h, 37 \degree C) with anti-TNF-\alpha at concentrations (5.75–10.45 \mu g/ml) commensurate with TNF-\alpha levels in the sol samples. Parallel incubations of NHBE cell cultures with anti-TNF-\alpha were used as controls.

Alternatively, to confirm the effect of sputum sol TNF-\alpha, rh-TNF-\alpha was added to NHBE cells at a concentration corresponding to TNF-\alpha levels (1.15–2.09 ng/ml) in individual sputum sol samples. The effect of rh-TNF-\alpha on IL-6 secretion into the medium was compared with those due to incubations with sputum sol samples.

Treatment of NHBE cells with anti-inflammatory drugs

To further study the potential effects of various anti-inflammatory drugs on the stimulated IL-6 production, NHBE cells (lot 8F0258) were pre-incubated (1 h, 37 \degree C) with one of four anti-inflammatory drugs: dexamethasone (stock solution, 100 mg/ml in methanol; working, 4 ng/ml (0.01 \mu M)), 40 ng/ml (0.1 \mu M) and 400 ng/ml (1 \mu M)), ibuprofen (stock solution, 100 mg/ml in methanol; working, 50 \mu g/ml (242 \mu M), 80 \mu g/ml (388 \mu M) and 100 \mu g/ml (485 \mu M)), triptolide (stock solution, 2.5 mg/ml in ethanol/acetone (1/1, v/v); working, 20, 200 and 1000 ng/ml) and MK-663 (0.1, 1 and 10 \mu g/ml). The drug concentrations were chosen based on data from previously published studies\textsuperscript{12–14} or from the supplier (Merck Research Laboratory for MK-663). The effect of drug vehicle on IL-6 production was also studied by pre-incubating NHBE cells with different concentrations of methanol, ethanol and acetone. The drug-treated cultures were then exposed either to sputum sol samples (at 50-fold dilution) or rh-TNF-\alpha (at concentrations comparable to that in the diluted sol samples) for another 4 h at 37 \degree C. After the incubation, the medium was recovered and the cell-free supernatant was assayed for IL-6. Results were compared with those of corresponding cultures incubated in control medium.

Statistical analysis

The IL-6 levels measured in the experiments were expressed as mean ± SEM. Statistical significance was tested by Wilcoxon signed ranks test for paired data
and Mann-Whitney U-test for independent data. Significance was accepted at \( P < 0.05 \). All the statistical tests were done by SPSS version 10.0 (SPSS Inc., Chicago, IL, USA).

**Results**

**Levels of TNF-\( \alpha \) and IL-6 in sputum sol samples**

Ten Chinese subjects (five males, age 54±15 years) with non-cystic fibrosis bronchiectasis were recruited. All subjects were never smokers. In all study subjects, HRCT scan of thorax showed features of cylindrical type diffuse bronchiectasis. The cause of bronchiectasis was classified as idiopathic in all cases. Secondary causes of bronchiectasis, including infections especially tuberculosis, congenital or acquired immunodeficiency and primary ciliary dyskinesia, were excluded. *Pseudomonas aeruginosa* was isolated from sputum in three cases, *Haemophilus influenzae* in one case and commensals in six cases. Lung function indices included forced expiratory volume in 1 s (FEV1) \( 6 \pm 4 \) L as predicted and forced vital capacity (FVC) \( 80 \pm 21 \) % predicted. Six subjects had their sputum sol samples measured for TNF-\( \alpha \) \( 1.55 \pm 0.34 \) ng/ml and the corresponding sputum IL-6 concentrations were undetectable (less than 10.24 pg/ml, the detection limit of the ELISA).

**TNF-\( \alpha \) in sputum sol stimulates IL-6 production by NHBE cells**

Exposure of cultures of NHBE cells to sputum sol samples \( (n = 10) \) found elevated IL-6 levels in the medium \( 1.9 \pm 0.2 \) times as high as that found in parallel incubations of NHBE cells in culture medium alone \( (45.6 \pm 29.1 \) pg/ml). As TNF-\( \alpha \) was invariably found in expectorated sputum samples of patients with bronchiectasis, attempts were made to neutralize its effect by pre-incubation of the sol samples with commensurate levels of a polyclonal antibody against human TNF-\( \alpha \). Exposure of NHBE cells to antibody-treated sol samples indeed resulted in IL-6 levels almost as low as those of cells exposed simply to the culture medium \( (1.1 \pm 0.1 \) times, \( P > 0.05 \) compared to control). To confirm that the sputum-stimulated effect was due to TNF-\( \alpha \), cells were exposed instead to rh-TNF-\( \alpha \) at a concentration corresponding to the mean TNF-\( \alpha \) found in the sputum sol samples. IL-6 concentration in rh-TNF-\( \alpha \)-treated cultures was found to be \( 5.3 \pm 0.6 \) times that of cells exposed to culture medium alone \( (P < 0.05) \). Thus TNF-\( \alpha \) is an important factor in the sputum cytokine network that stimulates IL-6 production by NHBE cells.

**Anti-inflammatory drugs vary in effects on IL-6 production by NHBE cells**

The effects of anti-inflammatory drugs on TNF-\( \alpha \)-mediated IL-6 production in NHBE cells were then studied. Consistently, rh-TNF-\( \alpha \)-stimulated IL-6 production by NHBE cells could effectively be down-regulated by all four anti-inflammatory drugs—dexamethasone, ibuprofen and MK-633 brought levels down to 2–3 times that in control medium whereas triptolide remained the most effective in that IL-6 levels could be lowered to 60% of that in control medium (Fig. 1).

Similarly, experiments were also performed to test for drugs that can counter the IL-6 production by sputum-stimulated NHBE cells. Sputum sol samples obtained from all 10 subjects with idiopathic bronchiectasis were used for the experiments. Among the drugs tested, dexamethasone (4–400 ng/ml) showed no suppressive effect on sputum-stimulated cell production of IL-6 (Fig. 2A). Instead of inhibition, an additional increase in IL-6 level, at 15–20% above those indicated by sputum-stimulated cells was detected in media of cells treated with dexamethasone \( (P > 0.05) \).

Although ibuprofen (50–100 \( \mu \)g/ml), a non-steroidal anti-inflammatory drug (NSAID), could to an extent counter sputum-stimulated IL-6 production, IL-6 levels remained at 1.5–1.8 times as high as those of cells in the control medium (Fig. 2B). The NHBE cells, however, appeared more responsive to treatments with the two experimental drugs, MK-663 (COX-2 inhibitor) and triptolide. MK-663 (0.1–10.0 \( \mu \)g/ml) resulted in dose-dependent suppression of sputum-stimulated IL-6 production, to levels that approach that of cells in the control medium (Fig. 2C). Triptolide (20–1000 ng/ml) also resulted in dose-dependent suppression of sputum-stimulated IL-6 production, but to levels as low as 24% of cells in the control medium (Fig. 2D). Altogether, at the highest concentrations of drugs used in the experiments, triptolide (1000 ng/ml) had the greatest inhibitory effect on sputum sol-stimulated IL-6 production. On the other hand, pre-incubation of NHBE cells with drug vehicles (methanol, ethanol, acetone) at different concentrations showed no significant effect on IL-6 production (data not shown).
Discussion

In this study, we have demonstrated that sputum sol samples from subjects with bronchiectasis contain stimulatory factors for IL-6 production by NHBE cells in vitro, and identified that TNF-\(\alpha\) in the sputum plays an important role in the induction of IL-6 production in bronchial epithelial cells. Among the anti-inflammatory drugs tested in the study, ibuprofen, a COX-2 inhibitor MK-663 and triptolide but not dexamethasone showed clear inhibitory effects on IL-6 production from bronchial epithelial cells after stimulation with sputum from bronchiectatic subjects.

TNF-\(\alpha\) has been isolated in significant levels in bronchiectasis, and has been found to be an important mediator in the cytokine network for tissue degradation. Several studies have suggested TNF-\(\alpha\) and IL-1\(\beta\) as the major stimulatory cytokines for IL-6 production in human bronchial epithelial cells and human airway smooth muscle cells. The stimulation with rh-TNF-\(\alpha\) in our study resulted in effective up-regulation of IL-6 production by NHBE cells, which was consistent with previous studies. The apparently more effective stimulation of IL-6 production with rh-TNF-\(\alpha\) than sputum sol samples could be due to inactivation of TNF-\(\alpha\) in sputum or presence of other cytokines in sputum that inhibit IL-6 production. On the other hand, pre-incubation of sputum sol samples with anti-TNF-\(\alpha\) antibody could drastically suppress IL-6 production from NHBE cells, approaching the basal level secreted by blank-stimulated cells. Since the action of anti-TNF-\(\alpha\) antibody is specifically targeted to TNF-\(\alpha\), the marked inhibitory effect of anti-TNF-\(\alpha\) antibody on IL-6 production suggests an important role of TNF-\(\alpha\) in the inflammatory cytokine network. This is analogous to the principle for recent anti-cytokine therapy in rheumatoid arthritis. The various pro-inflammatory cytokines interact with each other leading to propagation of inflammation. Basic and clinical studies have shown that application of neutralizing anti-TNF-\(\alpha\) antibody can effectively improve the inflammation in rheumatoid arthritis, which involves many other cytokines as well, such as IL-1, GM-CSF and IL-6. Therefore the loss of activity of one major mediator causes breakdown of the inflammatory network resulting in cessation of inflammation.
Since bronchiectasis is considered as an inflammatory airway disease, there has been great interest in the potential use of various anti-inflammatory drugs to overcome the inflammatory cascade. Dexamethasone, an analog of glucocorticoids, is a potent immunosuppressive agent and is widely used in airway inflammation-related diseases. There are studies showing that dexamethasone can effectively down-regulate the level of IL-6 production mediated by rh-TNF-α on human airway smooth muscle cells, lipopolysaccharide on monocyotic cell line, and rhinovirus on human tracheal epithelial cells.

In our study, dexamethasone showed no inhibitory effect on IL-6 production after stimulation with sputum sol samples from bronchiectasis subjects. However, in NHBE cells stimulated with rh-TNF-α, dexamethasone showed effective though incomplete suppression of IL-6 production. This suggests that despite effective down-regulation of IL-6 production by TNF-α with dexamethasone, there are stimulatory factors other than TNF-α in the sputum sol that are not inhibited by the action of dexamethasone. This supports the presence of a network of cytokines actively participating in the inflammatory process. Even when the major pro-inflammatory cytokine TNF-α is deactivated, other pro-inflammatory cytokines which go through alternative pathways are still working.

Ibuprofen, a NSAID, inhibits the enzyme cyclooxygenase (both COX-1 and COX-2) which is crucial in the formation of prostaglandins thereby leading to suppression of inflammation. It has been associated with an increased, decreased, or unchanged pro-inflammatory cytokine secretion. In particular, ibuprofen has been found to increase IL-6 in endotoxic mice, and decrease IL-6 in human peripheral blood mononuclear cells. A novel NSAID, lornoxicam, has also been found to suppress IL-6 production in lipopolysaccharide-

Figure 2 Inhibitory effects of anti-inflammatory drugs on IL-6 in sputum sol-stimulated NHBE cells. (A) Lack of inhibitory effect of dexamethasone at 4, 40 and 400 ng/ml on sputum sol-stimulated NHBE cells. (B) Ibuprofen at 50, 80 and 100 µg/ml suppressed IL-6 in sputum sol-stimulated NHBE cells. The inhibitory effect reached a plateau at ibuprofen concentration 50 µg/ml. (C) MK-633 at 0.1, 1 and 10 µg/ml suppressed IL-6 in sputum sol-stimulated NHBE cells. There was a dose-dependent inhibitory effect across the different concentrations of MK-633 tested. (D) Tiptolide at 20, 200 and 1000 ng/ml suppressed IL-6 in sputum sol-stimulated NHBE cells. There was a dose-dependent inhibitory effect across the different concentrations of triptolide tested. Statistically significant differences were indicated on the graphs. IL-6 levels were expressed relative to those in cells cultured in control medium (45.6 ± 29.1 pg/ml).
stimulated monocytic cells (THP-1). In fact, recent study suggested that ibuprofen inhibited the activation and translocation of the key transcriptional factor nuclear factor-kappa B (NF-κB) by blocking the degradation of inhibitor-κB-α, a protein that forms a complex with NF-κB, thus preventing the release and subsequent translocation of NF-κB into the nucleus and the expression of inflammatory cytokines. Our results support an inhibitory role of ibuprofen on IL-6 production from NHBE cells stimulated with bronchiecstatic sputum sol but this inhibitory effect reached a plateau at low concentration of the drug (50 μg/ml). Similar results could also be demonstrated in NHBE cells stimulated with rh-TNF-α.

Recent studies suggest that cyclo-oxygenase exists in a constitutive form (COX-1) and an inducible form (COX-2) in which the latter is predominantly related to inflammation. The use of selective COX-2 inhibitors has been proven to have potent anti-inflammatory actions while avoiding major adverse effects by preserving the COX-1 activity. Therapeutic administration of a selective COX-2 inhibitor, SC-58125, could rapidly reverse inflammation in rat adjuvant arthritis and reduce serum IL-6 and paw IL-6 mRNA levels to near normal levels. Similarly, in NHBE cells, we could demonstrate in this study an efficient and dose-dependent down-regulation of bronchiecstatic sputum sol-induced IL-6 production with a novel COX-2 inhibitor MK-663. This inhibitory effect on IL-6 was also found in NHBE cells stimulated with rh-TNF-α. Therefore, our results suggest the predominant role of COX-2 isoform in the airway inflammation related to bronchiecstatic.

Triptolide is a diterpenoid triepoxide purified from a Chinese herb Tripterygium Wilfordii Hook F (TWHF) which has long been used in traditional Chinese medicine for the treatment of leprosy and rheumatoid arthritis. It affects T cell activation through inhibition of IL-2 transcription at a site different from the target of cyclosporin A. It also up-regulates the mRNA expression of inhibitor-κB-α in a dose-dependent fashion thereby decreasing the NF-κB activity in T lymphocytes. In human bronchial epithelial cells, triptolide inhibits normal and transformed cell expression of IL-6 and IL-8 after stimulation by phorbol 12-myristate 13-acetate (PMA), TNF-α, or IL-1β. The results of this study demonstrated clearly that triptolide could efficiently down-regulate the IL-6 production from NHBE cells on stimulation with bronchiecstatic sputum sol. This inhibitory effect occurred in a dose-dependent fashion. Similarly, triptolide could also inhibit IL-6 production in NHBE cells stimulated with rh-TNF-α.

Despite recent works on the functions of IL-6 in various inflammatory models, the exact role of IL-6 has been controversial. IL-6 has been regarded to have both pro-inflammatory and anti-inflammatory properties. In acute infections, IL-6 may be an important mediator of acute phase reaction to defend against sepsis. In the setting of chronic disease especially in the presence of viral or bacterial infections, IL-6 serves as an important player in the elicitation of cellular immune responses against affected cells and of mucosal humoral responses against reinfection. However, an over-exuberant response may not be desirable in conditions like bronchiecstatic, where the response to microorganisms is up-regulated but ineffective in eradication of the organism, and many of the pathologic features are attributed to the severe inflammatory response. On the other hand, over-suppression of IL-6 production, as demonstrated by using triptolide at highest concentration, may also be detrimental. We have previously demonstrated significant reduction of sputum leukocyte density and IL-1β, IL-8 and LTB4 with inhaled corticosteroid (fluticasone) treatment in patients with non-cystic fibrosis bronchiecstatic. The exact implications of regulation of cytokine production with drugs in clinical management of bronchiecstatic should be further explored.

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References


