

Differences of Inflammatory Mechanisms in Asthma and COPD

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ABSTRACT

Bronchial asthma and chronic obstructive pulmonary disease (COPD) are increasing common diseases. The major pathogenesis of both illnesses is chronic inflammation. However, the inflammatory pattern is distinct in each disease. In asthmatic airways, activated mast cells/eosinophils and T helper 2 lymphocytes (Th2) are predominant. In contrast, macrophages and neutrophils are important in COPD airways/lung. Although nitric oxide (NO) hyperproduction due to inducible NO synthase (iNOS) is observed in asthma and COPD, nitrotyrosine formation via the reaction between NO and O₂⁻ in addition to the myeloperoxidase-mediated pathway. These distinct inflammatory patterns in both diseases seem to cause pathological differences in asthma and COPD.

KEY WORDS

bronchomotor tone, inflammatory cells, nitric oxide, oxidative stress, tachykinins

INTRODUCTION

Both bronchial asthma and chronic obstructive pulmonary disease (COPD) are defined as inflammatory diseases in recent worldwide guidelines,^{1,2} although the inflammatory process for each disease is different. In this review, I describe some differences in the inflammatory processes in each disease.

INFLAMMATORY CELL INFILTRATION

Bronchial asthma is characterized as chronic airway inflammation from the central to the peripheral airways involving various cell types such as activated mast cells/eosinophils and T helper 2 lymphocytes (Th2), which release mediators that contribute to asthma symptoms (Table 1).^{1,3-10} Actually, many cytokines and growth factors such as IL-4, IL-5, and GM-CSF can be monitored with exhaled breath condensate (EBC) (Table 2).¹¹ Clinically, examination of the eosinophil infiltration into the airways (sputum) is useful for discriminating asthma from COPD.^{12,13}

On the other hand, in COPD, the inflammatory cells that infiltrate into the airways/lung are different (Fig. 1).¹³ Macrophages are increased in the lungs of patients with asthma and COPD, however, they are more increased in COPD than in asthma. These macrophages are derived from circulating mono-

cytes, which migrate to the lungs in response to chemoattractants such as CC-chemokine ligand 2 (CCL2), also known as MCP1, acting on CCR2, and CXCL1 acting on CXCR2.¹⁴

Neutrophils are also increased in the sputum of patients with COPD and are correlated with the disease severity.¹⁵

However, during exacerbations in both diseases, inflammatory cell infiltration into the airways becomes less selective, that is, there is neutrophil infiltration in asthma and eosinophil accumulation in COPD, possibly due to virus-induced chemokine production via the epithelium.

MEDIATORS THAT ACT ON THE BRONCHOMOTOR TONE

In asthma, cysteinyl leukotrienes are potent bronchoconstrictors and proinflammatory mediators mainly derived from mast cells and eosinophils. They are the only mediator whose inhibition has been associated with an improvement in lung function and asthma symptoms.^{1,16} Histamine and prostaglandins are also released from mainly mast cells and contribute to the bronchomotor tone in asthma.¹ Therefore, functional antagonists, such as β 2-stimulants, cause more potent bronchodilation than anti-cholinergic agents in bronchial asthma.

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Table 1 Inflammatory cells in asthmatic airways

Mast cells: Activated mucosal mast cells release bronchoconstrictor mediators (histamine, cysteinyl leukotrienes, prostaglandin D₂) (3). These cells are activated by allergens through high-affinity IgE receptors, as well as by osmotic stimuli (accounting for exercise-induced bronchoconstriction). Increased mast cell numbers in airway smooth muscle may be linked to airway hyper-responsiveness (4).

Eosinophils, present in increased numbers in the airways, release basic proteins that may damage airway epithelial cells. They may also have a role in the release of growth factors and airway remodeling (5).

T lymphocytes, present in increased numbers in the airways, release specific cytokines, including IL-4, IL-5, IL-9, and IL-13, that orchestrate eosinophilic inflammation and IgE production by B lymphocytes (6). An increase in Th2 cell activity may be due in part to a reduction in regulatory T cells that normally inhibit Th2 cells. There may also be an increase in invariant T cells, which release large amounts of T helper 1 (Th1) and Th2 cytokines (7).

Dendritic cells sample allergens from the airway surface and migrate to regional lymph nodes, where they interact with regulatory T cells and ultimately stimulate the production of Th2 cells from naïve T cells (8).

Macrophages are increased in the airways and may be activated by allergens through low-affinity IgE receptors to release inflammatory mediators and cytokines that amplify the inflammatory response (9).

Neutrophils are increased in the airways and sputum of patients with severe asthma and in smoking asthmatics, but the pathophysiological role of these cells is uncertain and their increase may even be due to glucocorticosteroid therapy (10).

Reproduced from reference 1.

Table 2 Relative cytokine levels to positive control in exhaled breath condensates (EBC) obtained from either healthy subjects (a) or asthmatic subjects (b)

Cytokine	Control subjects (%) ^(a)	Asthmatic subjects (%) ^(b)	Fold increase ^(b/a)	Cytokine	Control subjects (%) ^(a)	Asthmatic subjects (%) ^(b)	Fold increase ^(b/a)
IL-1 α	4.0 \pm 2.1	5.2 \pm 1.3	1.30	IL-8	5.4 \pm 2.1	8.3 \pm 1.9*	1.52
IL-1 β	4.6 \pm 0.9	4.2 \pm 2.0	0.92	Mig	4.2 \pm 1.4	4.1 \pm 1.5	0.97
IL-2	4.9 \pm 1.7	4.1 \pm 2.0	0.83	IP-10	8.4 \pm 1.3	22.7 \pm 6.4*	2.72
IL-3	5.7 \pm 1.4	5.0 \pm 2.0	0.88	I-309	3.5 \pm 1.5	3.5 \pm 2.2	1.00
IL-4	5.2 \pm 1.7	8.2 \pm 1.6*	1.56	MIP-1 α	6.3 \pm 1.3	9.2 \pm 2.0*	1.47
IL-6	5.2 \pm 1.2	4.7 \pm 1.7	0.91	MIP-1 β	6.5 \pm 1.5	10.2 \pm 3.7*	1.58
IL-6sR	5.1 \pm 1.3	4.6 \pm 1.8	0.91	MIP-1 δ	3.7 \pm 1.3	5.4 \pm 2.9	1.45
IL-7	2.6 \pm 0.8	3.2 \pm 1.5	1.24	RANTES	6.2 \pm 1.5	10.4 \pm 2.5*	1.69
IL-10	5.4 \pm 1.8	5.7 \pm 1.6	1.04	MCP-1	6.5 \pm 2.1	7.9 \pm 2.2	1.20
IL-11	5.6 \pm 1.8	5.2 \pm 1.8	0.93	MCP-2	4.1 \pm 1.7	4.3 \pm 1.5	1.04
IL-12 p40	4.8 \pm 1.4	4.2 \pm 1.8	0.88	Eotaxin-1	4.6 \pm 2.2	5.0 \pm 2.3	1.09
IL-12 p70	2.8 \pm 1.4	3.4 \pm 2.1	1.24	Eotaxin-2	3.9 \pm 1.7	4.3 \pm 1.3	1.11
IL-13	4.0 \pm 1.0	5.5 \pm 2.3	1.37	G-CSF	3.6 \pm 1.7	3.1 \pm 1.5	0.88
IL-15	7.3 \pm 2.8	7.4 \pm 3.4	1.01	GM-CSF	3.8 \pm 1.0	3.4 \pm 1.6	0.92
IL-16	6.2 \pm 1.8	6.5 \pm 4.3	1.04	M-CSF	9.7 \pm 3.4	9.4 \pm 4.7	0.97
IL-17	8.6 \pm 1.5	12.6 \pm 4.1*	1.46	TGF- β	6.6 \pm 1.2	11.6 \pm 3.4*	1.69
TNF- α	7.0 \pm 1.0	12.4 \pm 3.8*	1.76	PDGF	6.8 \pm 1.6	7.6 \pm 1.8	1.12
TNF- β	27.7 \pm 7.4	27.6 \pm 8.3	1.00	TIMP-2	9.5 \pm 2.9	9.0 \pm 3.0	0.94
sTNF RI	4.8 \pm 1.8	5.4 \pm 1.4	1.13	ICAM-1	3.4 \pm 0.8	3.4 \pm 2.1	1.00
sTNF RII	5.1 \pm 1.6	4.6 \pm 1.5	0.90	IFN- γ	5.4 \pm 2.2	5.5 \pm 2.2	1.00

Abbreviations: Mig, monokine induced by IFN-g; IL-6sR, IL-6 soluble receptor; MCP, monocyte chemoattractant protein; G-CSF, granulocyte colony-stimulating factor; M-CSF, macrophage colony-stimulating factor; PDGF, platelet-derived growth factor; TIMP-2, tissue inhibitor of metalloprotease 2; sTNF-R, soluble TNF receptor; ICAM-1, intracellular adhesion molecule 1. * $P < .01$ compared with control subjects. Reproduced from reference 5.

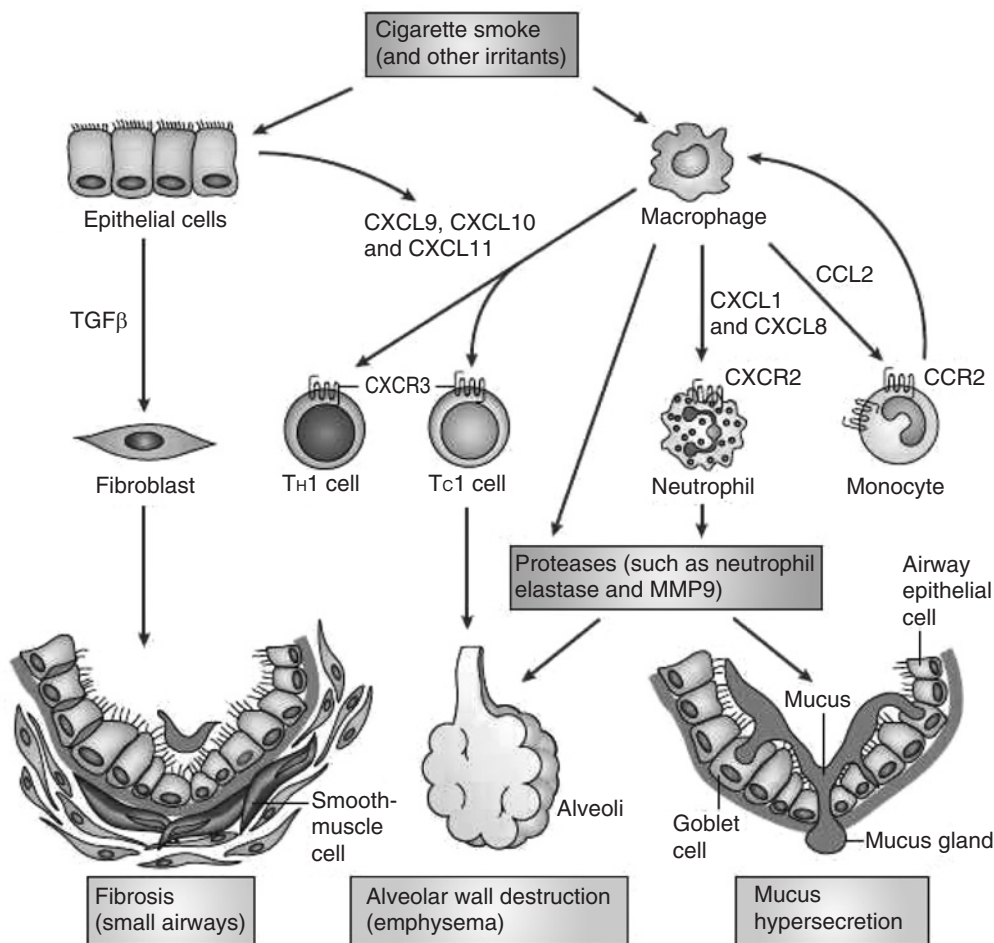


Fig. 1 Inflammatory cells involved in COPD. Inhaled cigarette smoke activates epithelial cells and macrophages to release several chemotactic factors that attract inflammatory cells to the lungs, such as CC-chemokine ligand 2 (CCL2), which acts on CC-chemokine receptor 2 (CCR2) to attract monocytes, CXC-chemokine ligand 1 (CXCL1) and CXCL8, which act on CCR2 to attract neutrophils and monocytes (which differentiate into macrophages in the lungs) and CXCL9, CXCL10 and CXCL11, which act on CXCR3 to attract T helper 1 (TH1) cells and type 1 cytotoxic T (TC1) cells. These inflammatory cells together with macrophages and epithelial cells release proteases, such as matrix metalloproteinase 9 (MMP9), which cause elastin degradation and emphysema. Neutrophil elastase also causes mucus hypersecretion. Epithelial cells and macrophages also release transforming growth factor- β (TGF β), which stimulates fibroblast proliferation, resulting in fibrosis in the small airways. Reproduced from reference 13.

In contrast, in COPD patients, such inflammatory mediators are not important for the bronchomotor tone. In COPD airways, anti-cholinergic agents shows more obvious bronchodilatory effects than β 2-stimulants, indicating that vagal nerve-derived acetylcholine is the only bronchoconstrictive (reversible) mechanism in this disease.¹⁷

TACHYKININS

Because tachykinins, such as substance P (SP) and neurokinin A (NKA), are potent stimulants of submucosal glands and goblet cell secretion,¹⁶ these peptides seem to be involved in the inflammatory process

in asthma and COPD. Increased SP concentrations have been reported in the induced sputum of patients with asthma and COPD compared with healthy individuals (Fig. 2).¹⁸ SP is metabolized by neutral endopeptidase (NEP),¹⁹ which exists in the respiratory epithelium. In asthmatic airways, epithelium shedding caused by eosinophil-derived major basic protein (MBP)^{20,21} leads to dysfunction of the NEP, which may enhance the tachykinins' function. Actually, there was a significant relation between the eosinophil count and SP concentration in the induced sputum from patients with asthma but not in that from COPD subjects.¹⁸ These data suggest that SP

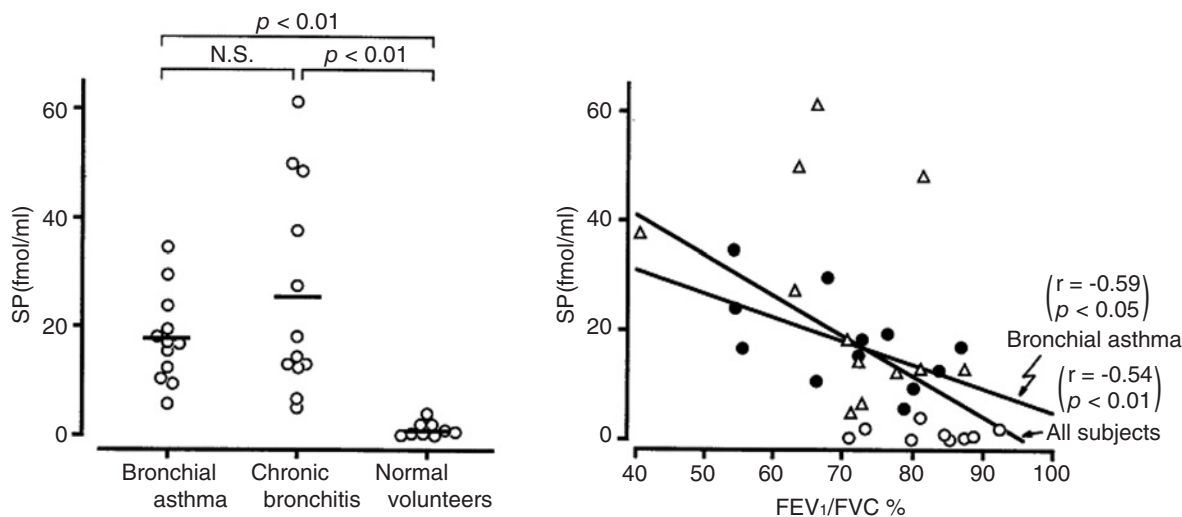


Fig. 2 Left panel: Substance P (SP) concentration in hypertonic saline-induced sputum. Bars indicate mean values. Right panel: Relation between SP concentration and FEV₁/FVC. *r* is correlation coefficient; the line and *p* value correspond to the fitted regression equation. Reproduced from reference 18 with modification.

hypo-degradation due to epithelial loss may be the cause of the elevated SP levels in asthmatic airways. Tachykinin antagonists have been administered to asthmatic subjects, and have shown clinical benefits in bradykinin- and exercise-induced asthma (Fig. 3, 4).^{22,23} There are no reported studies of tachykinin antagonists in COPD subjects.¹⁶

NITRIC OXIDE (NO) AND OTHER OXIDATIVE MOLECULES

Because reactive oxygen and related species including nitric oxide (NO) have a potent proinflammatory action,^{24,25} these molecules may be involved in the airway inflammatory process in asthma.²⁶ In animal models, allergen-²⁷ and ozone-induced²⁸ airway inflammation and airway hyperresponsiveness are largely modified by inhibitors of synthesis of reactive oxygen and related species or by scavengers of radical species, supporting this hypothesis. Further, NO hyperproduction due to inducible NO synthase (iNOS) has been shown in asthmatic airways and experimental asthma animal models.²⁹⁻³³ Steroid treatment reduces the NO generation,³⁴ suggesting that NO may be partly responsible for the asthmatic airway inflammation.

Other types of reactive oxygen, such as superoxide anion (O₂⁻) may also be exaggerated in asthmatic airways via the upregulation of xanthine oxidase (XO) in microvascular endothelial cells and NADPH oxidase in the infiltrated eosinophils.³⁵ NO rapidly reacts with O₂⁻ released from inflammatory cells including eosinophils, and results in the formation of the highly proinflammatory molecule peroxynitrite.³⁶

NO seems to be involved in the inflammatory mechanism of the late allergic response (LAR) after allergen challenge, which most resembles asthmatic

airway inflammation. We have assessed the NO, O₂⁻ and peroxynitrite production by measuring the NO concentration in the exhaled air, O₂⁻ generating enzyme activity, and peroxynitrite-induced nitration product immunostaining, respectively. We quantified the airway microvascular permeability by means of Monastral blue dye trapping between the postcapillary endothelium. The functional role of the NO, O₂⁻ and peroxynitrite on the microvascular permeability was assessed using each molecule's synthase inhibitor or scavenger. Further, we also quantified the eosinophil accumulation into the airways during the LAR and examined the role of NO, O₂⁻ and peroxynitrite in the eosinophil response. We have reported that peroxynitrite formed by NO and O₂⁻ is an important molecule for the microvascular hyperpermeability but not the eosinophil accumulation during the late allergic airway responses.³⁷

Oxidative stress and defense imbalance may be one of the causes of COPD.³⁸⁻⁴¹ The large production of NO during inflammatory-immune processes of the respiratory tract is thought to constitute a host defense mechanism, although this comes at a price because a high level of NO can also cause respiratory tract injury and thus contribute to the pathophysiology of inflammatory airway diseases such as COPD and asthma. Recently, excessive nitric oxide (NO) production, presumably via inducible NO synthase (iNOS), has been reported in asthmatic airways,⁴¹ although its presence is controversial in COPD airways.

The adverse effects of NO are thought to be engendered, in part, by its reaction with superoxide anion, which is released from inflammatory cells, yielding the potent oxidant peroxynitrite.³⁶ Peroxynitrite adds a nitro group to the 3-position adjacent to the hy-

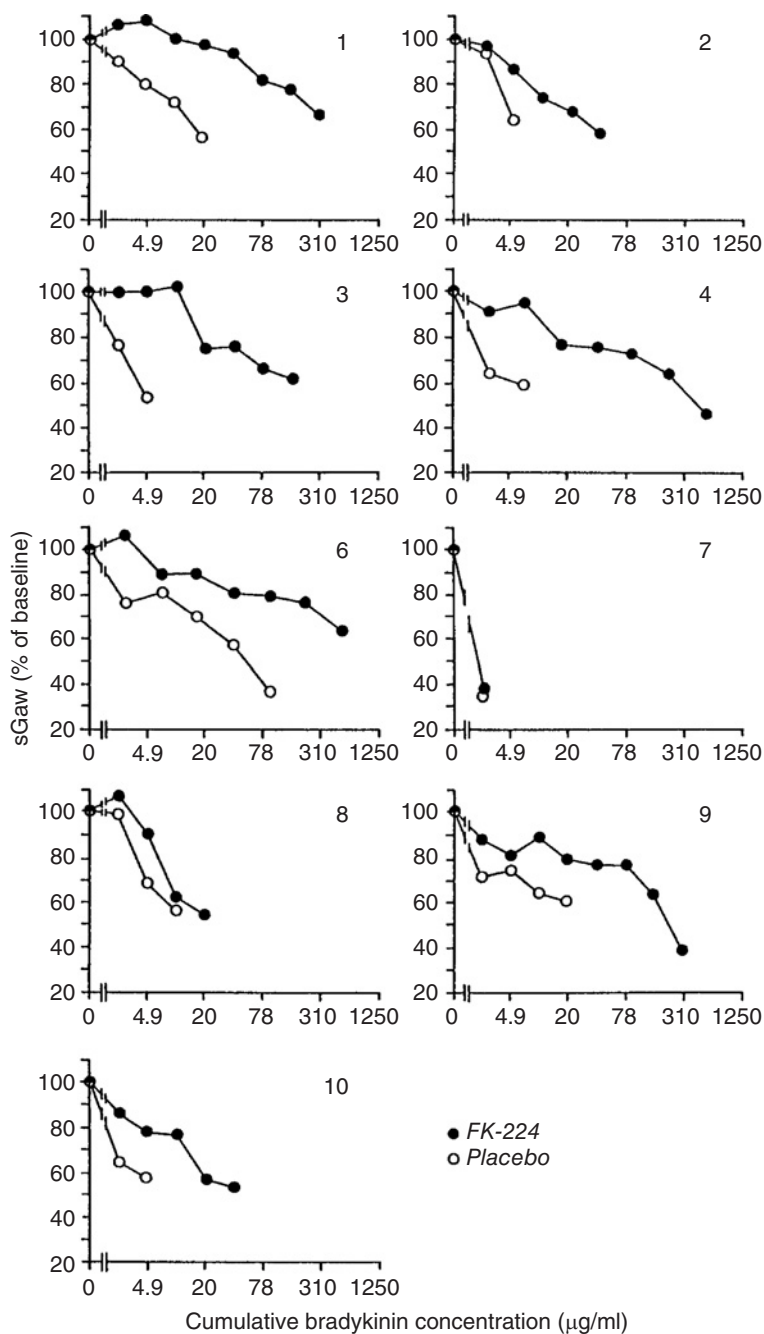


Fig. 3 Dose-response relation to bradykinin in each subject. ○ indicates after placebo and ● indicates after FK 224 (NK 1, 2-antagonist). Reproduced from reference 22.

droxyl group of tyrosine to produce the stable product nitrotyrosine. Alternatively, NO reacts with O₂ to form nitrite. The oxidation of nitrite by neutrophil-derived myeloperoxidase (MPO) or by other related peroxidases⁴² results in the formation of nitryl chloride and nitrogen dioxide (NO₂). This mechanism has also been found in inflammatory conditions. Although tyrosine nitration is generally attributed to peroxynitrite, the peroxidase-dependent nitrite oxida-

tion pathway is also involved. Therefore, nitrotyrosine is a collective indicator for the involvement of reactive nitrogen species. We have reported that abundant nitrotyrosine positive staining cells as well as iNOS positive cells were observed in the induced sputum both in COPD and asthmatic patients compared with healthy subjects.⁴³ The nitrotyrosine positive cells were significantly more obvious in COPD than in asthma, suggesting that the oxidative stress by reac-

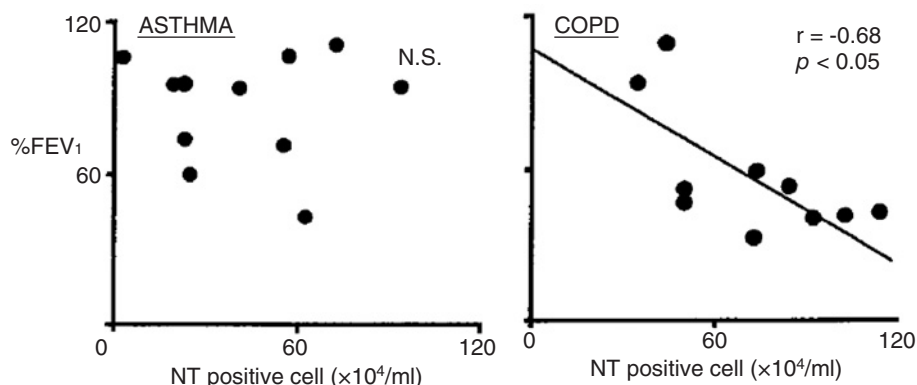


Fig. 4 Relation between %predicted FEV₁ and nitrotyrosine (NT)-positive cell counts in induced sputum of asthma and COPD patients. r is correlation coefficient; the line and p value correspond to the fitted regression equation. N.S., not significant. Reproduced from reference 43.

tive nitrogen species may be exaggerated in the airways of these diseases, especially in COPD. Further, because the nitrotyrosine positive cell counts were significantly correlated with the airway obstructive changes in COPD (Fig. 4),⁴³ the hyperproduction of reactive nitrogen species may be an important factor in the pathogenesis of COPD. Further, in COPD patients, the steroid-induced improvement in the airway caliber and hyperresponsiveness is significantly correlated with the reduction of the reactive nitrogen species production,⁴⁴ indicating that modulation of the reactive nitrogen species may be useful for future COPD therapy.

CONCLUSION

In this review, I have shown some aspects of the differences of the inflammatory processes in asthma and COPD. These differences seem to cause distinct pathological differences between the two diseases.⁴⁵

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