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AIRWAY VISTA 2014 POSTER ABSTRACTS

EFFECT OF MENTHONE TREATMENT BY INHALATION ON OVALBUMIN-SENSITIZED AND CHALLENGED ASTHMATIC MICE

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Introduction: Several studies have evidenced that terpenoids exert beneficial biological activities, such as anti-inflammatory, antioxidant, antimicrobial, and anticachexia effects. However, the effects of terpenoids on allergic asthma and possible mechanisms remain unclear.
Materials and Methods: To unravel the puzzle, a monoterpenoid menthone with anti-asthmatic potential was selected to treat ovalbumin (OVA)-sensitized and challenged BALB/c mice using inhalation intervention.
Results: In the present study our results showed that menthone intervention decreased serum OVA-specific and non-specific IgE antibody titers, Th2 cell derived cytokine production, eosinophilia, and mast cell degranulation. Furthermore, we found that menthone intervention significantly inhibited relative gene expression levels of *chemokine (C-C motif) receptor 3* and *chemokine (C-X-C motif) receptor 1* that are related to allergic inflammation in the lungs and airways. Our results suggested that menthone intervention by inhalation might decrease airway inflammation, mucin overproduction, and inflammatory cells infiltration and alleviate allergic inflammatory responses.

INHALATION TECHNIQUE ASSESSMENT IN RURAL SETUP IN INDIA AND EFFECT OF TECHNIQUE TRAINING

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Study Objectives: To investigate the inhalation technique of a rural population and study the effect of technique training.
Setting: A tertiary care hospital in North India located in a rural area.
Method: We assessed the inhalation technique of 89 COPD/Asthma patients. Patients with unsatisfactory technique were demonstrated the right technique and trained. The technique was again checked after a gap of 1 month.
Results: We studied 89 subjects (53 Males, 36 Females) with mean age 49.52 years (±10.28 years). 17 patients were using MDIs, 46 patients DPIs and 26 patients were using MDI with spacer. Only two (11.76%) patients were using MDI in appropriate way, while the corresponding values for DPIs and MDI with spacer were 21 (45.62%) and nine (34.61%). Education was the main predictor of right technique while age and sex had no effect on presence of appropriate technique. After teaching the proper technique, the technique was appropriate in four (23.53%), 36 (78.26%) and 14 (53.84%) patients.
Conclusions: DPIs are the better inhalation devices in the rural setup. The technique improves significantly after demonstrating the appropriate technique.

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THE TICK SALIVARY PROTEIN SIALOSTATIN L: A NEW TARGET FOR THE TREATMENT OF MAST CELL DEPENDENT ASTHMA?

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Abstract: Ticks developed multifaceted strategies for immune evasion in order to obtain a blood meal. One of the suppressive agents that was shown to be in tick saliva is the cysteine protease inhibitor sialostatin L[1]. In this study we can demonstrate that sialostatin L strongly impairs the production of the asthma promoting cytokine interleukin (IL)-9 by murine bone marrow derived mast cells (BMMC). Recently we could show that IRF4 (*interferone regulatory factor 4*) is a key molecule for the development of IL-9 producing T cells formally known as Th9 cells[2]. Additionally it was reported that IL-1β promotes the production of IL-9 in mast cells[3]. Therefore we studied the role of IRF4 and IL-1β regarding IL-9 production by BMMC after sialostatin L treatment. Initial "Next generation sequencing" of the transcriptome demonstrated that not only the *Il9*-expression but also the *Irf4*- and *Il1b*-expression is severely reduced upon treatment of BMMC with sialostatin L compared to untreated BMMC. In correlation with these findings, genetic ablation of *Irf4* or *Il1r1* (*IL-1 receptor 1*) strongly impairs IL-9 production by BMMC. Complementary, "chromatin immune precipitation" analyses revealed that IRF4 binds to the *Il9* promoter of stimulated BMMC. In line with this, *Il9* promoter reportergene studies clearly show that IRF4 plays a prominent role in driving the *Il9* promoter activity. Furthermore, treatment with sialostatin L renders mice resistant to experimental asthma. Our data clearly demonstrate that sialostatin L represses mast cell derived IL-9 via targeting IL-1R1 signaling and moderates asthma symptoms. Hence, the elucidation of the mechanisms underlying the immunosuppressive potency of sialostatin L could be the basis for the development of new strategies for the treatment of allergic asthma.

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KININ B1 RECEPTOR INHIBITION IN AIRWAY INFLAMMATION

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Rationale: Acute and chronic inflammatory airway diseases such as acute lung injury and bronchial asthma are major contributors to the global burden of diseases. Kinins are proinflammatory peptides that mediate a variety of pathophysiological responses through stimulation of two pharmacologically distinct receptor subtypes B1 and B2. The kinin B1 receptor is normally weakly expressed, but it is up regulated in the presence of cytokines and endotoxins or during tissue injury. Kinin B1 receptor represents a novel therapeutic target for inflammatory diseases. The aim of the present study was to demonstrate that kinin B1 receptor is a novel therapeutic target for the treatment of acute and chronic airway inflammatory diseases.
Methods: The anti-inflammatory effects of novel B1 receptor inhibitor BI 11382 were evaluated in experimental models of endotoxin-induced acute lung injury and in ovalbumin-induced asthma in mice.
Results: Intratrachal injection of endotoxin caused severe lung injury as evidenced by an excessive inflammatory cell infiltration in the lungs of vehicle-treated animals, compared to sham animals. The numbers of total cellular infiltrates and neutrophils in the lungs induced by endotoxin were significantly reduced in mice treated with B1 receptor inhibitor BI 113823. Treatment of B1 receptor inhibitor significantly reduced polymorphonuclear leukocytes accumulation and water content in the lung, and reduced total protein content and IL-1β level in lavage fluid, compared to vehicle controls. Ovalbumin sensitized mice showed an excessive increase in total cell counts, and numbers of eosinophils, macrophages and neutrophils. Treatment of B1 receptor inhibitor significantly reduced the numbers of eosinophils, macrophages, and neutrophils in the lungs instilled by ovalbumin. Treatment with B1 receptor inhibitor BI 113823 also significantly reduced total protein content and IL-1β in lavage fluid.
Conclusion: The present study shows that kinin B1 receptor inhibition is a powerful intervention to attenuate airway inflammatory in both experimental models of endotoxin-induced acute lung injury and in ovalbumin-induced asthma in mice.

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CLINICO-PATHOLOGICAL STUDY OF ADENOVIRUS ASSOCIATED WITH COMMUNITY ACQUIRED PNEUMONIA IN EGYPTIAN PATIENTS

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Background: Recently rigorous community acquired pneumonia due to viral pathogens has raised concerns. Little data are available as the association of adenovirus with community acquired pneumonia in Egyptian patients and its clinical and radiological features.
Aim: To study the clinico-pathological aspects of adenovirus associated with community acquired pneumonia in Egyptian patients.
Material and Methods: One hundred and four consecutive immunocompteenting with community acquired pneumonia were subjected to full clinical, radiological and microbiological studies to define the causative pathogens associated with pneumonia. Laboratory diagnosis of adenovirus relay upon high and/or serological conversion to adenovirus and presence of adenovirus DNA in sputum samples.
Results: Bacterial causes for pneumonia was identified among 53.8%. Positive virological markers for adenovirus were detected in 37.5% of the studied patients, Table 1. Patients with adenovirus pneumonia typically reported flu-like symptoms. Some of them developed shortness of breath or rigorous dyspnea on 7–9 days after disease onset. The patients with customarily present dyspnea and bilateral, mutilobal consolidation and patchy/ground-glass opacities. Risk factors analysis for association of pneumonia with adenovirus showed statistically higher prevalence in younger patients less than 40 years and associated with heftily ponderous smoking, Table 2.
Conclusion: Adenovirus represents a mundane pathogen for community acquired pneumonia in Egyptian patients that should meticulously be investigated for. Cumbersomely hefty smokers and puerile adults age carried higher risk for such condition.

Table 1 Clinico-Pathological finding among studied patients

Parameter		
Sex		
Male (No.–%)	65	62.5%
Age mean ± SD	45 ± 2.5	
Positive adenovirus markers	39	37.5%
Positive PCR (No.–%)	20	19.2%
Positive seroconversion (No.–%)	39	37.5%
Severity of clinical symptoms(No.–%)		
CURB score 65-severe (No.–%)	20	19.2%
Radiological finding (No.–%)	104	100%
patchy/ground-glass opacities (No.–%)	40	38.5%

Table 2 Risk Factors analysis associated with adenovirus

Risk Factor		P
Age	>40 years	P = 0.0001
Duration	<7 days	P = 0.0001
Smoking	40 per days	P = 0.0001

RELATIONSHIP BETWEEN PLASMA OREXIN-A, GHRELIN LEVELS, BODY COMPOSITION ASSESSMENT AND THE DISEASE SEVERITY IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) PATIENTS

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Aim: The aim of the study was the determination of relationship between plasma orexin-A, ghrelin levels, nutritional assessment, body composition and, the disease severity in stable Chronic Obstructive Pulmonary Disease (COPD) patients.
Materials and Methods: This study was consisted of 32 stable COPD patients, with an age of 44–80 years, who were admitted to Department of Pulmonary Disease in Gazi University Medical Faculty in a time period of June 2012 to June 2013. Subjective Global Assessment (SGA) was performed by the dietitians. Body composition (fat percentage, fat free mass) was measured by using "InBody 720" Bioelectrical Impedance Analyzer (BIA). Also waist circumference of patients was measured with suitable method. Blood samples were taken after 8–12 hours of fasting and plasma orexin-A and ghrelin levels were measured by ELISA. COPD staging was determined according to GOLD criteria (revised 2011). The patients were classified two groups, as "low risk" if their GOLD class were A and B and "high risk" if their GOLD class were C and D. The relation with plasma orexin-A and ghrelin levels, body composition and COPD GOLD classes were evaluated.
Results: According to GOLD classification, 34.4% of patients in Group A, 6.2% in Group B, 43.8% in Group C and 15.6% in Group D. Average plasma ghrelin levels were 26.19 ± 6.50 ng/mL and orexin-A levels were 1.32 ± 0.28 ng/mL. The differences mean orexin A (1.28 ± 0.20 ng/ml and 1.32 ± 0.32 ng/mL) and ghrelin levels (25.02 ± 6.36 ng/ml and 26.50 ± 6.81 ng/mL) of low and high risk groups COPD patients were not statistically significant (p = 0.753 and p = 0.686, respectively). There was not a significant difference between mMRC scores ≥2 and mMRC <2 groups' plasma orexin-A and ghrelin levels (p = 0.508 and p = 0.285, respectively). Similarly, it was not found significant difference orexin A and ghrelin levels according to number of attacks in last year (p = 0.554 and p = 0.106, respectively). No statistically differences were found in SGA scores, according to low or high risk groups (p = 0.362), mMRC scores groups (p = 0.698) and number of attacks in last year (p = 0.870). The mean body mass index (BMI), waist circumference, fat percentage and free fat mass of patients were not observed different according to low or high risk groups, mMRC scores groups and number of attacks in last year (Table 1).
Conclusion: Further studies are needed to understand the effect of plasma ghrelin, orexin-A levels, body composition and nutritional status on clinical course of patients with COPD.

Table 1 Some anthropometric measurements according to GOLD classification, mMRC and number of attacks

	BMI (kg/m^2)		Waist circumference (cm)		Fat percentage (%)		Free fat mass (kg)	
	X ± SD	p	X ± SD	p	X ± SD	p	X ± SD	p
GOLD classification								
Low risk	26.84 ± 4.10	0.445	98.00 ± 10.44	0.092	31.71 ± 7.70	0.486	50.05 ± 6.39	0.529
High risk	28.43 ± 5.26		104.74 ± 14.66		34.00 ± 6.97		52.03 ± 9.30	
mMRC								
<2	27.61 ± 4.50	0.721	101.21 ± 14.07	0.521	32.27 ± 6.86	0.320	52.47 ± 7.87	0.262
≥2	28.50 ± 6.13		105.83 ± 11.39		35.85 ± 8.14		47.54 ± 8.89	
Number of attacks								
<2	27.93 ± 5.06	0.788	101.98 ± 14.26	1.000	33.42 ± 7.62	0.686	51.33 ± 8.55	0.957
≥2	27.39 ± 4.24		103.17 ± 11.25		32.03 ± 5.80		51.08 ± 7.70	

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THE BURDEN OF ASTHMA AND COPD IN BRAZIL

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Aim: To present data regarding hospitalizations and deaths resulting from chronic obstructive lung disease (COPD) and asthma in Brazil during the last decades.
Method: Data was obtained from the Brazilian official hospital records system (DATASUS), which includes those hospitals financed by the Public Health System (PHS), and from the Brazilian official mortality system (SIM). For data from 1992–97, we used ICD 490, 491, 492, 493 and 496 (Revision 9 of the International Classification of Diseases (ICD)) and for the period since 1998, the ICDs J40, J41, J42, J43, J44, J45 and J46 (Revision 10 of the ICD).
Results: During 1992–2006, respiratory diseases ranked 8th among the main reasons for hospitalizations, being responsible for 15% (13–17%) of all hospitalizations financed by the PHS. While COPD was responsible for an average of 237,779 hospitalizations per year (12% of all hospitalizations for respiratory diseases and 2% of the total number of hospitalizations financed by the PHS) or an estimated 651 per day (a mean cost of US$ 54 millions per year, or an average of US$ 226 per hospitalization during that period, for PHS), asthma was responsible for 328,620 hospitalizations per year (900/day). This figure represented a rate of 1774 per 100,000 population, being slightly higher amongst females. In most cases, ICD J45 was the diagnostic classification used for the hospitalization (88% vs 12%).

Considering only the patients whose hospitalizations were caused by COPD, this disease caused an average of 93,660 deaths, or 4% of all COPD hospitalizations. The largest number of hospitalizations was observed amongst those aged 50 or more (86%). When gender differences were considered, COPD was more prevalent in males than females (65%).

Asthma hospitalizations showed a downward trend (5% per year). Hospital mortality rate was low (0.3%). For PHS, asthma hospitalizations represented an average cost of R$103.5 million per year, which increased during that period (7% per year). Hospital mortality was 0.3%. The highest medium hospitalization coefficient occurred amongst those aged less than five years of age, followed by those aged 55 or more; which may indicate misdiagnosis with COPD.

During 1980–2006, COPD was responsible for a mean 22,010 deaths per year, or an average of 60 deaths per day. These figures are about 10 times more than the rate for asthma (2118–6 per day) during the same period. For the whole period, there was an increasing trend (1980 = 9358; 2004 = 35,548). Overall, the death rate per 100,000 habitants was 14.12; with more deaths amongst males (17.93/100,000 *vs* 10.38/100,000 females). 84% of the deaths were amongst those aged 55 or more. 79% of the deaths occurred in a hospital environment. Overall, asthma death coefficient per 100,000 habitants was 1,5; there were slightly more deaths amongst females (1.7/100,000 females *vs* 1.3/100,000 males). Over the whole period, there was a downward trend of 0,2% per year. 16% of the deaths occurred amongst children younger than 5 years old and 58% of the deaths were among those aged 55 and over. It can be supposed that the higher proportion of deaths occurring in health units (72%) reflects low grade of efficient ambulatory care for the asthmatic population.
Conclusions: Exacerbations of asthma resulted in a thousand daily hospitalizations and an average of 6 deaths per day during the period studied, at a cost of R$ 100 million per year for the PHS with hospitalizations. Both the number of hospitalizations and the cost remained stable over the time period of the study. Children aged less than five years were the most affected. On the other hand, COPD was responsible for a great number of hospitalizations financed by the PHS during 1992–2006 in Brazil. Overall, PHS spends a mean US$ 54 million with more than 230,000 hospitalizations per year. The mortality rate during hospitalization is around 4%.

During 1980–2006, while asthma was responsible for an average of 6 deaths per day and COPD for an average of 58 deaths per day; One third of the reported deaths from asthma occurred amongst children younger than 15 years and more than half of the deaths were reported among those older than 55. Around 84% of deaths reported as caused by COPD were amongst adults over the age of 55. Undoubtly, COPD is a major cause of death amongst adults at Brazil, mainly for men. Almost 80% of the deaths occurred in hospital, which may reflect less of the population having access to effective ambulatory care.

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COMPARISON OF METHYLATION PROFILES IN HUMAN BLOOD AND LUNG TISSUE IDENTIFIES TISSUE SPECIFIC CpG METHYLATION SITES

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Introduction: We hypothesize that differences in methylation patterns between individuals may contribute to the etiology of asthma, COPD and other lung related traits. Most genetic studies collect and maintain blood samples from study participants, blood is likely to be the most widely available resource for studies looking to investigate the relationship between phenotype and methylation status. Given our interest in pulmonary phenotypes, and the knowledge that methylation patterns are tissue specific we wanted to identify CpG sites that demonstrate tissue specific methylation (TSM) patterns between blood and lung tissues.
Methods: To evaluate TSM we used 36 paired samples (blood and lung tissue from the same individual) and 22 lung only samples. Methylation of 450 thousand CpG sites throughout the genome was evaluated using the Infinium HumanMethylation450K bead chip array. Methylation levels were assessed using beta values which range from 0 (no methylation) to 1 (complete methylation). Principal components were used to identify 3 samples which clustered differently all 3 samples were noted to have low and/or poor quality DNA and were removed from subsequent analyses. Correlations between beta values were examined using principal components, heatmaps, and a mixture model of three distributions (unmethylated, variable methylation, complete methylation).
Results: We identified 49,376 CpG sites with apparent tissue specific methyation (see Table 1). There are 31 CpG sites with extreme differences in methylation, at these sites there is complete methylation in lung tissue but no methylation in blood tissue. We further identified 4541 CpG sites that are unmethylated in lung tissue, and demonstrate intermediate (variable) methylation patterns in blood tissue, 34,974 CpG sites with complete methylation in blood amd intermediate levels of methylation in lung tissue and finally 9830 sites where there is complete methylation in lung tissue and intermediate levels in blood tissue. Next we evaluated specific genes which have associated in genome-wide association studies with lung related diseases. We noted good correlation between blood and lung methylation values at *ORMDL3* asthma locus but poor concordance at sites with the Thymic Stromal Lymphopoietin (*TSLP*), see Figure 1.
Conclusion: We have identified 49,376 CpG sites with tissue specific methylation including CpG sites in the asthma gene *TSLP*.

Table 1 Correlations Between CpG Site Classifications in Blood and Lung Tissue

Lung vs. Blood Mixture Model Classification		Lung			Total
		Complete	Inter	No	
Blood	Complete	150,637 (33.98%)	34,974 (7.89%)		185,611
	Inter	9,338 (2.11%)	102.730 (23.18%)	4,541 (1.02%)	116,609
	No	31 (0.007%)	14,655 (3.31%)	126,366 (28.51%)	141,052
	Total	160,006	152,359	130,907	443,272

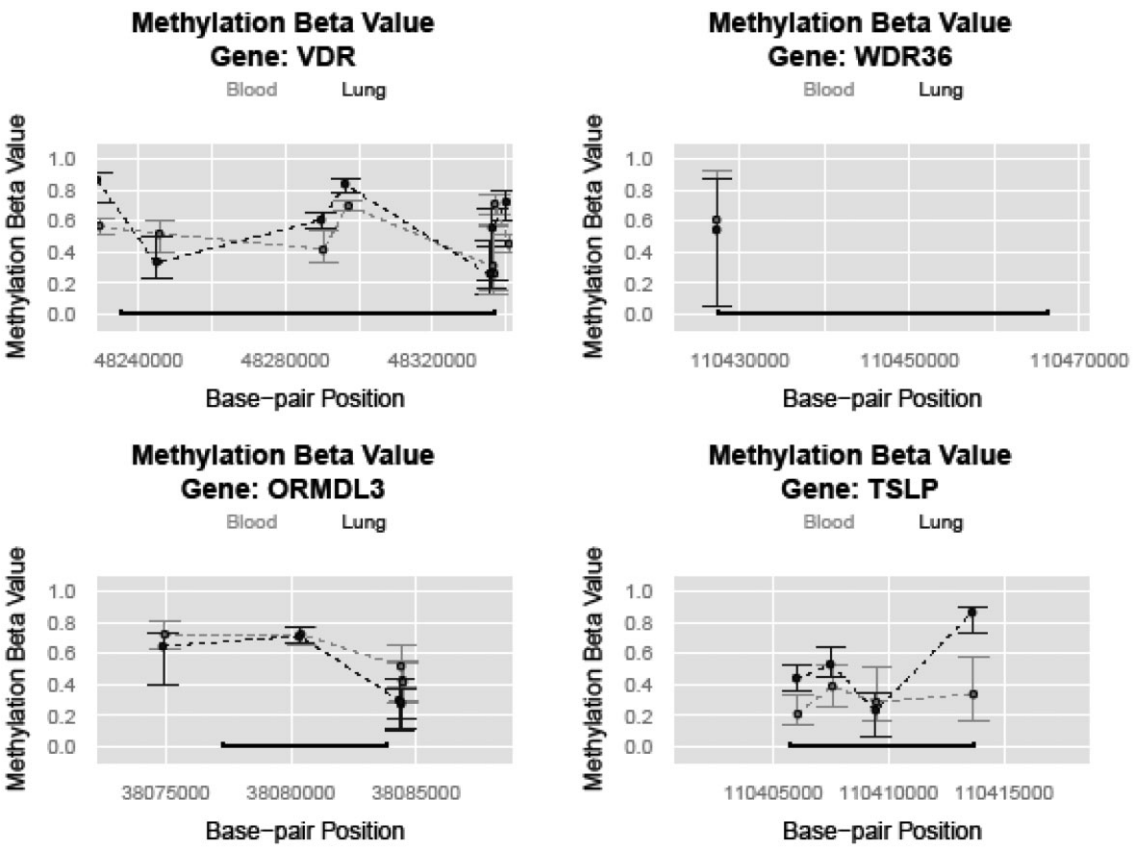


Figure 1 Lung Specific Candidate Genes.
Legend: red points (grey points) represent mean methylation values for blood at a particular site and blue (black points) is for lung. The error-bars drawn represent the middle 95% range of the distribution of beta values. We can see that for many of these genes (VDR, WDR36 and ORDL3) there distributions overlap, where as for TSLP there is a clear distinction between blood and lung tissue.

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BRONCHO-CONSTRICTION MEDIATED BY ACTIVATED T CELLS IN HUMANS AND MICE

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Introduction: To delineate IgE-independent mechanisms of asthma, T cell dependent bronchial constriction was investigated using an *in vitro* contraction assay of human bronchial smooth muscle cells (BSMCs). In mice, T cell-transfer model was analyzed for immediate and late phase asthmatic responses after antigen challenge.
Method: Peripheral blood mononuclear cells (PBMC) obtained from nonatopic asthmatics were cultured with secreted aspartic proteinase 2 (SAP2), a purified protein derived from *Candida albicans.* Cytokine concentration of the culture supernatants was measured by specific ELISAs. A contraction assay using collagen gels embedded with cultured human BSMCs was employed to analyze the contractile responses induced by the supernatants. Ovalbumin (OVA) specific Th clones were derived from either the regional lymphnodes of Balb/c mice immunized with OVA/CFA or splenocytes of DO11.10 transgenic mice expressing T cell receptor specific for OVA/H-2d. Th clones were adoptively transferred into unprimed mice. After intranasal or inhalation challenge with OVA, airway resistance was continuously monitored by either unrestrained whole body plethysmography (BUXCO) or resistance/compliance analyzer under anesthetized condition. Bronchoalveolar lavage and analysis of airway hyperresponsiveness (AHR) were performed 48 hr after OVA challenge. Supernatants of stimulated Th clones were analyzed for contractile activity using collagen gels embedded with murine primary BSMCs.
Results: PBMC obtained from several nonatopic asthmatics produced significant amount of IL-5, IL-13, and IFN-gamma upon incubation with SAP2 (responders). Upon bronchial challenge with SAP2, late but not immediate bronchial response was induced for the responders. Neither IAR nor LAR was detectable for the control asthmatics (nonresponders). IgE-dependent mechanism was ruled out by negative RAST, histamine releasing test, or immediate skin reaction. Anti-SAP2 IgG antibody (precipitin) was not detectable. The supernatants of PBMC cultured with SAP2 and CD3-stimulated Th clones induced a significant contraction of the gels embedded with cultured hBSMC. When unprimed mice were transferred with Th clones, T5-1, T6-2, T6-4, and T6-7, Penh values were significantly increased 6 hr after OVA challenge. In contrast, mice transferred with other Th clones, BF7, T6-1, or T6-10 did not show any change. Airflow limitation was confirmed by a direct measurement of airway resistance under anesthetized, restrained, and intubated conditions. The airflow limitation was also efficiently induced by the challenge with T cell epitope peptide, OVA323-339. Contractile activity was detected in the supernatants of T6-2 stimulated with immobilized anti-CD3.
Conclusion: Activation of Th cells resulted in an airflow limitation besides eosinophilic inflammation, AHR, and mucous hyperplasia. T cell-derived bronchoconstrictor might be a target for treatment-resistant asthma.

NICOTINE EXPOSURE ABROGATES RESPIRATORY TOLERANCE BY MODULATING TOLEROGENIC DENDRITIC CELLS AND REGULATORY T CELLS

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Intranasal exposure to allergen leads to the development of immune activation or, in the absence of inflammatory signals, respiratory tolerance protecting against airway hyper-reactivity (AHR), a cardinal feature of asthma. Identifying specific signals that can affect the delicate balance between airway tolerance and inflammation is important in the understanding of respiratory tolerance pathway and in designing new therapies for patients with asthma and other lung diseases. However, such factors and their impact on immune system remain largely unknown. Although the adverse effects of active cigarette smoking on the respiratory tract have been extensively characterized, the effects of nicotine exposure on induction of respiratory tolerance have not yet been investigated in detail. We show here, in a mouse model of allergen tolerance, that nicotine exposure during the induction of tolerance abrogates respiratory tolerance instead leading to an enhanced development of AHR with greater lung inflammation and mucus production. This breakdown of respiratory tolerance induced by nicotine exposure was associated with a decreased development of IL-10 producing tolerogenic dendritic cells (DC) and $Foxp3^+$ regulatory T cells (Treg) in mice. Nicotine exposure also induces modifications in the surface expression of activation markers on pulmonary DCs thus inducing polarization of $CD4^+$ T cells to Th2 rather than Tregs *in vitro*. As nicotine has been found to reflect the effects of cigarette smoke on the immune system, this study will help to understand why tolerance induction therapies are less efficient in patients actively or passively exposed to cigarette smoke.

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PROSTAGLANDIN E_2 STIMULATES NORMAL BRONCHIAL EPITHELIAL CELL GROWTH THROUGH INDUCTION OF PDK1 EXPRESSION: PRO-ONCOGENIC ROLE OF c-JUN

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Introduction: Cyclooxygenase-2-derived prostaglandin E_2 (PGE_2), a bioactive eicosanoid, is implicated in many biological processes including reproduction, inflammation and tumor growth. We previously showed that. PGE_2 stimulated lung cancer cell growth and progression through PGE_2 receptor EP2/EP4-mediated multiple kinase signaling pathways. However, the role of PGE_2 in controlling lung airway epithelial cell phenotype remains unknown.
Methods: The human non-small cell lung cancer (NSCLC) cell lines H1838 and H358 were obtained from the American Type Culture Collection and grown in RPMI 1640 supplemented with 10% heat – activated fetal bovine serum, HEPES buffer, 50 IU/mL penicillin / streptomycin, and 1μg amphoterincin (complete medium). Cells were plated into six-well culture plates at an initial seeding density of 5×10^4 cells per well. The plates were incubated in a humidified atmosphere of 5% CO_2 in air at 37°C.Lipofectamine 2000 reagent was purchased from Invitrogen. The CellTiter-Glo Luminescent Cell Viability Assay kit was purchased from Promega. Polyclonal antibodies against PDK1 and phosphorylated PDK1 (ser 241) were purchased from Cell Signaling. The polyclonal antibody against c-Jun was purchased from Santa Cruz Biotechnology, Inc. Polyclonal antibody against EP4, 16, 16-Dimethyl-PGE_2 (dmPGE2) and AH23848, OSU-03012 were purchased from Cayman Chemical Co.
Results: Here, we demonstrate that PGE_2 increased the normal bronchial epithelial cell proliferation through induction the protein expression of 3-phosphoinositede dependent protein kinase-1 (PDK1), an ankyrin repeat-containing Ser/Thr kinase implicated in the induction of apoptosis and the suppression of tumor growth. PDK1 small interfering RNA (siRNA) and inhibitor (OSU03012) blocked the effects of PGE_2 on normal cell growth. In view of its perceived importance, we turned our attention to the mechanisms involved in PGE_2-induced PDK1 expression and found that was blocked by an antagonist of the PGE_2 receptor subtype EP4 and by EP4 siRNA. In addition, we showed that induction of PDK1 by PGE_2 was associated with induction of transcription factor, c-Jun protein expression. Silencing of c-Jun using siRNA and point mutations of c-Jun sites in the PDK1 promoter resulted in blockade of PDK1 expression and promoter activity induced by PGE_2. Furthermore, overexpression of c-Jun induced the expression of PDK1 protein, promoter activity and cell proliferation. In conclusion, PGE_2 increases normal bronchial epithelial cell proliferation through increased PDK1 expression that is dependent on EP4 and induction of c-Jun in the PDK1 promoter. This study unveils a novel role of c-Jun and PDK1 in mediating pro-oncogenic effect of PGE_2 in the control of pre-malignant phenotype in normal bronchial epithelial cells.

A SINGLE DOSE OF INHALED SALMETEROL DOES NOT MITIGATE ENDOTOXIN-INDUCED HUMAN AIRWAY NEUTROPHILIA OR ITS MEDIATORS

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Introduction: Long-acting β_2-agonist, salmeterol, although predominantly a bronchodilator, may have anti-inflammatory properties that explain its well-attested clinical efficacy in asthma and COPD. We investigated this possibility by testing whether pretreatment with a single dose of inhaled salmeterol could mitigate endotoxin-induced human airway neutrophila.
Methods and Subjects: In a double-blind, cross-over, placebo-controlled study, ten healthy human subjects underwent two 15 μg of lipopolysaccharide (LPS) *(Escherichia coli serotype 026:B6)* inhalation challenges pretreated with a single dose of either 50 μg salmeterol or placebo delivered by accuhaler. Induced sputum and blood were collected one week prior (as baseline), six hours and one week after challenge. The two challenges were separated by 4 to 6 weeks. Standard clinical responses were also collected on the LPS inhalation challenges.
Results: Compared to placebo, salmeterol had no effect on the increase of sputum total cell counts [mean difference (SEM) salmeterol vs. placebo: 18.4 (9.3) vs. 15.2 (4.2) x 10^6 cells/ml; $p = 0.72$] or neutrophils [17.9 (9.3) vs. 13.8 (3.8) x 10^6 cells/ml; $p = 0.65$] induced by LPS challenge at 6 hours. Salmeterol also did not significantly alter the increase of sputum sol MPO protein [mean difference (SME): 426 (214) vs. 335 (107) ng/ml; $p = 0.81$], HNE activity [2.6 (1.6) vs. 1.9 (0.7) mOD/min; $p = 0.59$] and interleukin-8 [1168 (464) vs. 796 (273) pg/ml; $p = 0.33$] caused by LPS compared to placebo. The same were observed for blood total white cell counts and neutrophil counts. Temperature rise and symptoms induced by inhaled LPS was comparable in both salmeterol and placebo phases. At one week, all sputum cellular profile had returned to baseline levels.
Conclusions: A single dose of salmeterol does not appear to mitigate LPS-induced human airway neutrophilia or its mediators in healthy human subjects. Instead, there appear to be a trend towards an increased neutrophilia and its mediators following salmeterol. Our observations may shed light on cellular interactions between high affinity β_2-agonists and airway innate immunity during encounters with bacterial infections.

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EFFECTS OF INPATIENT PULMONARY REHABILITATION FOLLOWING ACUTE EXACERBATION OF COPD IN A SINGAPORE HOSPITAL

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Background: There is growing evidence that pulmonary rehabilitation (PR) immediately following an acute exacerbation of chronic obstructive pulmonary disease (COPD) improves exercise capacity and reduces hospital admissions in people with COPD. However, no studies on effects of PR after an acute exacerbation have been done in Singapore.
Methods: A retrospective analysis of our inpatient PR programme was performed over a year since its induction. Medically stable patients after an acute exacerbation of COPD stayed for a further two weeks and underwent 20 physiotherapy exercise sessions, 3 occupational therapy sessions and a diet counselling session. Six-minute walk tests (6MWT) and COPD Assessment Test (CAT) were administered pre and post inpatient PR. Readmission to hospital for COPD exacerbation within 30 days was also analysed.
Results: Of 22 COPD patients enrolled for inpatient PR, 19 patients completed the programme. Mean (SD) FEV_1 of these patients were 39 (11)%. Mean [95% confidence interval] change in distance walked in the 6MWT and in CAT scores were 50 [41 to 59] metres ($p < 0.01$) and -5 [-6 to -4] ($p < 0.01$) units respectively. Eight out of 10 patients who were admitted at least once every month in two consecutive months did not readmit within 30 days following inpatient PR program.
Conclusion: Clinically significant improvements in exercise capacity and health status and less patients readmit within 30 days were seen following early inpatient PR program in patients with acute exacerbation of COPD.

THE ROLE OF IFN-γ/MAST CELL AXIS IN THE PATHOGENESIS OF ALLERGIC INFLAMMATION IN ACUTE VERSUS CHRONIC MOUSE MODELS OF ASTHMA

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Introduction: Mast cells (MCs) play a critical role in the pathogenesis of allergic asthma, and the mechanisms which regulate the expression of MC function in asthma remain incompletely understood. The purpose of this study was to investigate the role of an IFN-γ/MC axis in the development of phenotypic features in models of acute and chronic asthma in mice.
Materials and Methods: In this study, wild type C57BL/6 mice, MC-deficient C57BL/6-*Kit* $^{W\text{-}sh/W\text{-}sh}$ mice, and C57BL/6-*Kit*$^{W\text{-}sh/W\text{-}sh}$ mice engrafted with bone marrow-derived and cultured MCs (BMCMCs) from wild type C57BL/6 or C57BL/6-IFN-γR1$^{-/-}$ mice were subjected to allergen sensitization and challenge following the protocol developed by us for inducing acute or chronic models of asthma in mice[1,2].
Results: In the acute model of asthma, the IFN-γ/MC axis was found to significantly enhance the development of airway hyperreactivity (AHR) and airway eosinophilia, but did not influence the antigen-driven increase in number of goblet cells. In the chronic model of asthma, the IFN-γ/MC axis was found to significantly regulate the development of AHR, airway eosinophilia/neutrophilia, as well as airway modeling, including the antigen-driven increase in number of goblet cells and lung collagen content[3].

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CELL THERAPY BY ADIPOSE STROMAL CELLS AFFECT TRACHEAL RESPONSIVENESS AND INFLAMMATORY RESPONSES IN GUINEA PIGS MODEL OF COPD

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Chronic obstructive pulmonary disease (COPD) is a worldwide epidemic disease known as a leading cause of death in the world. In the present study, the effects of adipose derived stromal cells (ASCs) on tracheal responsiveness and immunological parameters in guinea pigs model of COPD were evaluated. Thirty six guinea pigs were randomized divided into 6 groups including: Control, COPD, COPD + intratracheal delivery of PBS as vehicle (COPD + ITPBS), COPD + intravenous delivery of PBS as vehicle (COPD + IVPBS), COPD + intratracheal delivery of ASCs (COPD + ITASC) and COPD + intravenous injection of ASCs (COPD + IVASC). COPD was induced by exposing animals to cigarette smoke for 3 months. After 14 days of cell therapy, tracheal responsiveness as measured by effective dose of methacholine-induced 50% of maximum tracheal contraction (EC50), concentration of interleukin-8 (IL-8) in serum and broncho-alveolar lavage fluid (BALF), as well as total and differential white blood cells (WBC) counts were evaluated. Tracheal responsiveness, total WBC couts, nutrophil and eosinophil percentage in BALF as well as concentration of IL-8 in serum and BALF significantly increased but lymphocyte percentage decreased in COPD compared to the control group ($P < 0.05$ to $P < 0.001$). Cell therapy was able to restore the tracheal hyperresponsiveness, IL-8 in serum and BALF in COPD-ITASC but not in COPD-IVASC animals. However, total WBC in BALF a significantly decrease in both treated groups but the precentage of eosinophils, neutrophils and lymphocytes in BALF were reversed in COPD-ITASC compared to COPD-ITPBS animals ($P < 0.05$ to $P < 0.001$). In conclusion, intratracheal cell therapy with ASC can decrease tracheal hyper-responsiveness and respiratory inflammation in cigarette smoke induced-COPD. Therefore, it may be helpful in attenuation of the severity of disease in patients suffering from COPD.

Key words: Adipose; COPD; Guinea pigs; Tracheal responsiveness; Stromal cells; Cytokines, Lung Inflammation

EFFECT OF MISHANDLING OF INHALERS ON MANAGEMENT OF PATIENTS WITH ASTHMA

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Introduction: Incorrect usage of inhaler devices might have a major influence on the clinical effectiveness of the delivered drug. The objective of this study was to assess the incorrect technique with established inhalers in patients with asthma, to highlight the common errors observed in inhalation technique and to discuss implications for clinical efficacy.
Materials and Methods: Firstly, recruited patients completed a standardized questionnaire; each questionnaire consisted of a general section and specific parts, each related to a specific inhaler. Then, each patient demonstrated the inhalation technique with all used devices to the investigator in a quiet area using a placebo device.
Results: We have collected 100 records of inhaler technique. At least one critical mistake was widely distributed among users of all the inhalers, ranging from 19% for Evohaler®, 19% for Accuhaler®, and 29% for Turbuhaler®. We found the strongest association between inhaler misuse and older age ($p = 0.01$), lower schooling ($p = 0.01$) and lack of instruction or check-up received for inhaler technique by health caregivers ($p = 0.03$). Inhaler misuse was associated with increased risk of hospitalization ($p < 0.001$), emergency room visits ($p < 0.001$), courses of oral steroids ($p < 0.001$) and antimicrobials ($p < 0.001$) and poor disease control evaluated as an Asthma Control Test (ACT) score for the asthma ($p < 0.001$).
Conclusions: Inhaler mishandling continues to be common in experienced outpatients referring to chest clinics and associated with increased unscheduled health-care resource use and poor clinical control. Instruction by health caregivers maybe the modifiable factor useful for reducing inhaler mishandling.

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NOVEL ROLE FOR INTERLEUKIN-6 TRANS-SIGNALING IN THE PATHOGENESIS OF PULMONARY INFLAMMATION AND EMPHYSEMA

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Introduction: Lung inflammation triggered by cigarette smoking is strongly linked to emphysema, a major component of the debilitating Chronic Obstructive Pulmonary Disease (COPD). Considering immune regulators are likely to influence emphysema susceptibility, we have recently shown that expression of the potent immunomodulatory cytokine interleukin (IL)-6 is consistently increased in emphysema patients, and increased IL-6 expression in a genetic mouse model for spontaneous emphysema (*gp130*$^{F/F}$) drives the onset of lung disease[1]. Although IL-6 signals using 2 distinct modes, classical signalling via its membrane-bound IL-6 receptor (mIL-6R), and trans-signaling (TS) via a naturally-occurring soluble IL-6R (sIL-6R), the precise mechanism(s) by which IL-6 promotes emphysema remains to be elucidated.
Methods: The *gp130*$^{F/F}$ emphysema mouse model was used to measure the gene and protein expression status of specific IL-6 signalling components, and genetic and therapeutic blockade of IL-6TS in these mice was employed to prove the specific role of IL-6TS in driving disease. Findings were validated in human lung tissue biopsies.
Results: sIL-6R production is elevated in the lungs of emphysematous mice, and is coincident with up-regulation of ADAM17 which is responsible for proteolytic cleavage of mIL-6R to produce sIL-6R. Transgenic over-expression of the IL-6TS antagonist sgp130Fc blocks the development of pulmonary inflammation and emphysema in *gp130*$^{F/F}$ mice. Notably, IL-6TS-driven emphysema correlated with augmented alveolar cell apoptosis in *gp130*$^{F/F}$ mice. Furthermore, we demonstrate that exposure of wild-type mice to cigarette smoke leads to excessive sIL-6R production and alveolar cell apoptosis, the latter of which is blocked by pre-treating mice with sgp130Fc. Finally, we also reveal that IL-6, ADAM17 and sIL-6R are up-regulated in human lung tissue from emphysema patients.

Collectively, our data reveal that specific targeting of IL-6TS may represent a new therapeutic strategy for emphysema/COPD.

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STUDY OF COPD HIGH RISK GROUP PATIENTSAT ONE UNIVERSITY HOSPITAL IN INCHEON

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Mortality of COPD high risk group patients is very poor. But study about this group is still unknown to us in Korea. Retrospectly, we studied characterictics, pulmonary function test and laboratory findings about mortality of COPD high group patients. Patients who met the current consensus of COPD definition and high group(one or more hospitalizations for COPD exacerbations) were enrolled from April 2000 to June 2013 in Gachon University Gil Medical Center in Inchon, Korea. Retrospectively, we analyzed the clinical characteristics, pulmonary function test and laboratory findings. Total 859 patients were enrolled. Survival group were 40 patients. Death group were 21 patients. COPD has been divided mild (4.7%), moderate 34.9%, severe 37.2% and very severe 23.3% by the Global Initiative for Chronic Obstructive Lung Disease (GOLD). GOLD 3 stage about one or more hospitalizations for COPD exacerbationso ccurred frequently compared with GOLD1 or 4. Comorbidities was significantly higher in death group than survival group (3 vs 1.88, $p = 0.006$). Most common comorbity was cardiovascular disease.CRP and neutrophil (%) in stable state was significantly higher in death group than survival group ($p = 0.025$, $p = 0.026$). Lymphocyte(%) in stable state was significantly lower in death group than survival group ($p = 0.003$). Neutrophil (%) in hospitalization was significantly higher in death group than survival group ($p = 0.025$). Lymphocyte (%) in hospitalization was significantly lower in death group than survival group ($p = 0.011$). The two groups have no significant difference in pulmonary function test. In high risk group of COPD, Comorbidities and laboratory findings should be looked for routinely, and treated appropriately.

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RELATIONSHIP OF BETWEEN S100A9 (S100 CALCIUM BINDING PROTEIN A9) AND NEUTROPHILIC SEVERE ASTHMA

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Background: We demonstrated that elevation of S100A9 protein in sputum of neutrophilic severe uncontrolled asthmatics by ELISA experiments (Accepted in Annels of allergy, asthma, immunology on June. 2013). Neutrophilic severe asthma is attributed to the altered expression of biologically relevant proteins. Therefore, S100A9 may play an important role in neutrophilic severe asthma.
Objectives: The aim of this study was to validate the identified proteins in neutophilic severe asthma model such as Cryptogenic Fibrosing Alveolitis, OVA and Normal controls.
Methods: Cell numbers were measured by Diff-quick staining and were response to methacholine (MCh) measured using the in vivo CFA-sensitized/ challenged mice and sham model. The mRNA and protein levels of S100A9 and S100A8 were measured using a RT-PCR, Real-time PCR and western blot. Protein localizations were measured by Immunohistochemical (IHC) stain and Immunofluorescene(IF) stain. Airway inflammation of S100A9 protein was confirmed the neutrophil in BAL fluid cells and lung tissue.
Results: The Numbers of neutrophil cells in BAL fluids and airway hyperresponsiveness (AHR) of CFA-sensitized/ challenged mice were significantly increased compare with sham-treated mice. The mRNA and protein levels of S100A9 and S100A8 were higher in CFA-sensitized/challenged mice than OVA and sham-treated mice. S100A9 protein was expressed on inflammatory cells of peribronchiolar area and on bronchial epithelial cells. Intra –tracheal of administration S100A9 induced neutrophilic inflammation.
Conclusion: Role of the S100A9 protein may be induces to neutrophilic severe asthma. S100A9 protein is specific to neutrophilic inflammation of asthma and crucial for the development of neutrophilic inflammation in the airways.

CLINICAL CHARACTERISTICS OF NON-SMOKING PATIENTS WITH COPD IN KOREA

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Background: Chronic obstructive pulmonary disease (COPD) is caused by chronic exposure to environmental factors in genetically susceptible individuals. Although cigarette smoking is known as a major risk factor, emerging evidence suggests that other environmental exposure can influence COPD. The purpose of this study is to investigate clinical characteristics of non-smoking patients with COPD.
Methods: The study population comprised 135 patients who were recruited from a cohort that consisted of Korean COPD subjects living near cement plants, termed COPD in dusty area (CODA). We evaluated the frequency of respiratory symptoms, pulmonary function, quality of life questionnaire, environmental exposure, and CT phenotypes of self-reported never smoking patients with COPD, comparing with smoked patients. Biomass fuel exposure was evaluated using the question, "For cooking and/or heating, have you ever been exposed to biomass fuels such as wood, agricultural crop residues, animal dung, charcoal, and others.
Results: 103 patients reported history of smoking, 32 reported never smoked. Male was 100 (97.1%) among smokers and 4 (12.5%) among never-smokers. Post-bronchodilator forced expiratory volume on one second (FEV_1) was 77.9 ± 19.4 (% of predicted, mean $\pm$ standard deviation) in smokers, 84.6 ± 23.2 in never smokers. Biomass fuel exposure was 46 (44.7%) among smokers, compared with 23 (71.9%) among never smokers.
Conclusion: COPD patients without history of cigarette smoking in Korea were more prevalent in female, had poor lung function, and had more exposure history of biomass fuel. Our data suggest that environmental factors other than cigarette smoking may influence clinical phenotype of COPD.

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PREVALENCE OF ADENOMATOUS COLORECTAL POLYP IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Background: The smoking is the most common cause of chronic obstructive pulmonary disease (COPD). Colon cancer is an increasing fatal disease, also the smoking is known as a cause of colon cancer. The adenomatous colon polyps are precancerous lesion of colorectal malignancy. But no study has evaluated the association between colorectal malignant potential with COPD. The aim of this study was to assess the prevalence of adenomatous colorectal polyps in COPD patients and whether COPD is associated with colorectal malignant potential.
Methods: From our hospital database between January 2003 and April 2012, we searched subjects, who were 40 years old and more and performed both of post-bronchodilator spirometry and colonoscopy. COPD was defined as having a ratio of forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) < 0.7 in post-bronchodilator spirometry. Non-COPD group was matched age and gender, and defined as having a FEV_1, FVC and $FEV_1/FVC \geq 0.7$ in spirometry. Finally, two-hundred eighty five patients were retrospectively reviewed and data of age, gender, height, weight, smoking history and co-morbidities collected. Eighty-two patients had COPD. We analyzed colonoscopic results and pathologic findings.
Results: The mean age was 65 years, and about 90% patients were male. One hundred sixty-three (80%) were non-smokers and 51 (25%) were current smokers in total patients. The prevalence of an adenomatous colorectal polyp was 43% (87/203) in non-COPD group and 72% (59/82) in COPD group. Nine patients were confirmed adenocarcinoma in total. Among 54 patients with adenomatous colorectal polyps in COPD group, 47 had tubular adenoma and 7 had villous adenoma by pathologic evaluation. Multiple logistic regression analyses revealed that COPD combined status (OR 1.98, 95% CI 1.06–3.7; p = 0.032) was independently associated with colorectal malignant potential (Table 1).
Conclusions: The risk of colorectal malignant potential in COPD patients was relatively high. COPD patients should be considered regular colonoscopic evaluation.

Table 1 Multivariate analysis of factors contributing to colorectal malignant potential

Variable	Hazard ratio (95% confidence interval)	p-value
Age	0.992 (0.957–1.028)	0.655
Male gender	2.624 (0.860–8.007)	0.090
BMI (kg/m^2)	1.054 (0.962–1.155)	0.257
Smoking status		0.936
Never smoker	1	
Current smoker	0.883 (0.433–1.800)	
Ex-smoker	0.932 (0.509–1.155)	
COPD combined	1.980 (1.062–3.691)	0.032

Multiple logistic regression analysis was adjusted by age, gender, BMI, smoking status, COPD combined. Colorectal malignant potential were mean both adenomatous polyps and adenocarcinoma on pathologic findings of colonoscopy. BMI: body mass index; COPD: chronic obstructive pulmonary disease.

PHENOTYPIC HETEROGENEITY AMONG SUBJECTS WITH GOLD SPIROMETRY GRADE 1

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Introduction: Chronic obstructive pulmonary disease (COPD) is well-known as a syndrome with many different disease-related characteristics and substantial phenotypic heterogeneity. Most previous studies have been limited to COPD patients with spirometry grade 2 or more defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD 2-4).However, subjects with GOLD 1 (post-bronchodilator $FEV_1 \geq 80\%$ predicted) make up a large proportion of COPD patients. The aim of this study was to investigate the heterogeneity in COPD subjects with GOLD 1.
Methods: We analyzed data fromcurrent and former smokers participating in the COPDGene Study. We compared GOLD 1 subjects according to (1) lower limit of normal for FEV_1/FVC(LLN) as a threshold;(2) the presence or absence of history of any respiratory exacerbations during the one year period before the study enrollment; and (3) significant emphysema (≥10% *vs.* <5% at -950 HU) measured by volumetric computed tomography (CT) of the chest. (4) K-means clustering was used to classify subjects within the GOLD 1 cohort.
Results: (1) The group of subjects meeting bothGOLD 1 and LLN-COPD criteriahad younger mean age, higher proportions of African Americans and current smokers, decreased body mass index (BMI) and increased total lung capacity measured by CT, and an increased prevalence of chronic bronchitis relative to LLN-normal GOLD 1 subjects (all $P < 0.05$). (2) Subjects with GOLD 1 and a history of any respiratory exacerbations were more likely to be female, and had increased segmental wall area %, higher MMRC dyspnea score, and increased prevalence of chronic bronchitis and physician-diagnosed asthma compared to those without a history of exacerbation in the past year (all $P < 0.05$). Except for oral corticosteroids, all respiratory medications were more frequently used in those with an exacerbation history (all $P < 0.01$). (3) Among subjects with significant emphysema (≥10%),there were more males, fewer current smokers, higher pack-years of cigarette smoking, lower BMI, and lower segmental wall area % compared with those without significant emphysema (<5%) (all $P < 0.05$). While neither exacerbation frequency nor severe exacerbation showed difference between these two groups, tiotropium was more frequently used in subjects with significant % emphysema ($P < 0.001$). (4) Four subgroups were identified by k-means clustering, aputative "highest FEV_1 % predicted", "airway-predominant", "emphysema-predominant" and the "lowest FEV_1 % predicted" subtypes.
Conclusions: Clinical heterogeneityis apparent within subjects with mild airflow obstruction.Although longitudinal follow-up of GOLD 1 heterogeneityis needed for clinical application, each subtype may need a different therapeutic goal,leading to specific treatments.

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CHINESE HERBAL MEDICINE FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Introduction: Chinese herbal medicines (CHM) are used by up to 20% of people with chronic obstructive pulmonary disease (COPD)[1]. Despite this, there is no conclusive evidence supporting the routine use of CHM for COPD.
Methods: We conducted a systematic review to evaluate randomised controlled trials using CHM for the treatment stable COPD and acute exacerbations of COPD. All types of publications were included, such as published trials, thesis and abstracts. Evaluated outcomes were lung function (FEV1, FVC), symptom severity (BORG, mMRC), health related quality of life (SGRQ), exercise capacity (6MWT), exacerbation rate and adverse events. The methods of the overview were in line with the Cochrane Collaboration and methodological quality was assessed using the Cochrane Risk of Bias Tool.
Results: In total, 252 studies were included. Due to the large number, studies were grouped into two categories; CHM versus any control (placebo, routine pharmacotherapy, or no treatment) and CHM plus routine pharmacotherapy (RP) versus RP alone. Overall CHM appeared to be very well tolerated and safe. Efficacy was difficult to determine due to the use of various formulae and herbs, as well as heterogeneity in study design and methodological shortfalls. Despite these limitations CHM appeared to significantly improve outcomes of clinical relevance, including health related quality of life, short-term lung function, and dyspnoea.
Conclusions: This review indicates that CHM may provide some benefit to people with COPD. Further evidence is still needed in larger studies that evaluate CHM over a longer period and include follow-up data as well as rigorous study designs. The routine use of CHM for COPD using a particular formula or herb cannot be deduced from this review. However, CHM appears to be safe and further studies are needed to explore their potential as treatments for COPD.

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