Review Article on Pollutional Haze

Pollutional haze and COPD: etiology, epidemiology, pathogenesis, pathology, biological markers and therapy

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Abstract: In recent years, serious pollutional haze occurs in the mainland of China thanks to the development of urbanization and industrialization. There is a close relationship between air pollution and the occurrence and development of chronic obstructive pulmonary disease (COPD), but there are some new characteristics in some aspects of COPD associated with pollutional haze compared with COPD induced by traditional physical and chemical factors. This article attempts to summarize the new progress from these new features of COPD related to pollutional haze, focus on etiology, epidemiology, pathogenesis, pathology, biological markers and therapy.

Keywords: Chronic obstructive pulmonary disease (COPD); pollutional haze; etiology; pathogenesis; biological markers; therapy

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Pollutional haze is a combination of fog and haze. It is commonly not only in the city but also in rural areas. Many China areas incorporated fog into haze as disastrous weather forecast, collectively referred to as the "haze weather". The haze weather is an atmospheric pollution; haze is the general statement, which is a mixture of fog and particles exceeding atmosphere circulatory self-purified ability. Particles size less than 2.5 micron are thought to be responsible for haze weather. Haze is the result of the interaction of the specific climatic conditions and human activities, such as automobile exhaust, factory air pollution, coal combustion, destruction of forests, volcano eruption and sandstorm etc. The economic and social activities produce a large amount of PM2.5, if emissions exceed purified capacity of the atmospheric circulation, concentration of PM2.5 will continue to accumulate, at this time if the weather is calm, pollutional particles are easy to form a wide range of haze. The main composition of fog and haze are sulfur dioxide (SO_2), nitrogen oxides (NO_X) and particulate matter. The particulate matters are the main harmful components, but the SO_2, NO_X, ozone (O_3) and other harmful substances are also threatened to human health. Pollutional haze is closely related to some human disease, such as skin allergies, cardiovascular diseases (hypertension, coronary heart disease, pulmonary heart disease etc.), and respiratory diseases [respiratory infections, asthma, chronic obstructive pulmonary disease (COPD) etc.]. Serious pollution will cause death. Among all the systems and organs in our body, the respiratory tract is the commonest area to be involved in. In recent years, more and more people understand the seriousness of haze related COPD, and more and more clinicians and scientists have been devoting their time and efforts to study the association between haze and COPD. These researches have promoted our understanding of etiology, epidemiology, pathogenesis, pathology, biochemical indicators, and treatment strategies of COPD associated with pollutional haze.

In this review, we summarize the major developments in

recent years. We searched PubMed with the keywords 'haze' and 'COPD', 'air pollution' and 'COPD', 'PM2.5' and 'COPD', 'PM10' and 'COPD', 'SO_2' and 'COPD', 'NO_X' and 'COPD', 'O_3' and 'COPD', 'smog' and 'COPD', 'NH_3' and 'COPD', and found more than 500 references published during the last several years. Considering the length of this review, we selected original published researches and removed all reviews and meta-analyses. The original papers covered almost all research fields of 'haze and COPD', including etiology, epidemiology, pathogenesis, pathology, biomarkers and therapeutic approaches. Here, we review these achievements classified by etiology, epidemiology, pathogenesis, pathology, biomarkers and therapy.

Epidemiology and etiology

Epidemiological studies have evaluated various causes which can produce haze, for example, traffic-related air pollution, household air pollution, occupational exposure, and so on. And these studies also reveal the outcome of COPD related to haze through specific particles and molecules.

Automobile exhaust has an inescapable responsibility for formation of haze weather. Many scholars studied the effects of traffic air pollution on COPD. Gan *et al.* (1) investigated the associations of long-term exposure to elevated traffic-related air pollution and wood smoke pollution, meanwhile reported the risk of COPD hospitalization and mortality. This population-based cohort study included a 5-year exposure period and a 4-year follow-up period. During the exposure period, all residents aged 45–85 years who resided in Metropolitan Vancouver, Canada, did not have known COPD at baseline and were included in this study (n=467,994). Hospitalizations and deaths during the follow-up period were identified from provincial hospitalization and death registration databases. The authors reported that an interquartile range (IQR) elevation in black carbon concentrations ($0.97\times10^{-5}/m^3$, equivalent to 0.78 $\mu g/m^3$ elemental carbon) was associated with a 6% [95% confidence interval (CI): 2–10%] increase in COPD hospitalizations and a 7% (0–13%) increase in COPD mortality after adjustment for covariates. Exposure to higher levels of wood smoke pollution (tertile 3 *vs.* tertile 1) was associated with a 15% (2–29%) increase in COPD hospitalizations. In another study, Andersen *et al.* (2) assessed the effect of exposure to traffic-related air pollution over 35 years on the incidence of COPD in a prospective cohort study. They followed 57,053 participants in the Danish Diet, Cancer, and Health cohort in the Hospital Discharge Register for their first hospital admission for COPD between 1993 and 2006, and estimated the annual mean levels of nitrogen dioxide (NO_2) and NO_X at all residential addresses of the cohort participants since 1971 to 2006 and used indicators of traffic near the residential address at recruitment, finally, they concluded that long-term exposure to traffic-related air pollution may contribute to the development of COPD. Meanwhile, they also pointed out that different body height, different body weight, different ages, different pollution degree and other aspects should be considered when to study the influence of haze weather on COPD.

Farmers from many rural areas of developing countries in the world still use wood, coal for cooking, heating, so it is hardly to avoid indoor air pollution. The relationship between biofuel and COPD aroused many researchers' attention. Mejza *et al.* (3) analyzed data from 618 subjects, and identified an independent risk factor, that is, farmers might have lower FEV_1/FVC values compared to other occupational people as well as increasing COPD risk. Ultimately, they reported that the COPD incidence of Malopolska inhabitants exposed to risk factors associated with cooking or heating with coal or wood is significant high than that in other area inhabitants. In the studied population, farming was related to increased risk of COPD. Also, da Silva *et al.* (4) evaluated the effects on respiratory tract of biofuel combustion and compared the results with those individuals using liquefied petroleum gas (gas) from the same community in Brazil. They showed that chronic exposure to biofuel combustion was associated with increased prevalence of respiratory symptoms, reduced lung function and promoted the development of COPD. Speaks *et al.* (5) also found that smoke exposure to household air pollution was attributed to approximately 1/3 of deaths related to COPD in global. Interestingly, Johnson *et al.* (6) reported that COPD incidence was higher in biofuel users than that in the clean fuel users 2.5% *vs.* 2%, (OR, 1.24; 95% CI: 0.36–6.64) and it was two times higher (3%) in women who spend >2 hours/day in the kitchen involved in cooking. From January to June of 2009, Desalu *et al.* (7) carried out a cross-sectional study including 269 adult women. They used a questionnaire adapted from the European Community Respiratory Health Survey and all data were further analyzed according to different subgroups, which included sociodemographic status, type of fuel used for cooking in the household, respiratory symptoms, and smoking history. All of the participants were invited to undergo spirometry. Through the analysis of the study

results, they underscored the necessity of replacement of biofuel with a nontoxic type of fuel, such as electricity or gas.

Bushfire not only results in household air pollution, but also causes out-air pollution, which is consistent with haze. Here are some papers on wildfire smoke associated with COPD. Morgan *et al.* (8) investigated mortality and hospitalization of the inhabitants whose COPD's cause was from bushfire-derived particulates, compared with the people whose COPD's cause was related to particulates from urban sources in Sydney, Australia from 1994 through 2002. They assumed particulate matter with aerodynamic size <10 micron (PM10) was primarily from bushfires, calculated the contribution to the happening of COPD of bushfire PM10 by subtracting the background PM10 concentration estimated from surroundings. They found a 10 mg/m^3 increase in bushfire PM10 was associated with a 3.80% (1.40% to 6.26%) increase in COPD admissions (at lag 2). Similarly, Martin *et al.* (9) surveyed that correlation between air pollution from bushfires and hospitalization in Sydney, Newcastle and Wollongong, Australia 1994–2007. They reported that smoke events (smoke events were defined as days on which bushfire smoke caused the 24-hour citywide average concentration of airborne particles to exceed the 99 percentile of the daily distribution for the study period) occurred on 58 days in Sydney (population: 3,862,000), 33 days in Wollongong (population: 406,000) and 50 days in Newcastle (population: 278,000). In Sydney, events were associated with a 6% (OR, 1.06; 95% CI: 1.02–1.09) same day increase in respiratory hospital admissions same day COPD admissions increased 13% (OR, 1.13; 95% CI: 1.05–1.22). Rappold *et al.* (10) performed a population-based study and found that in the exposed counties, significant increases in cumulative RR for COPD [1.73 (1.06–2.83)] using emergency department (ED) visits through the syndromic surveillance program NC DETECT.

Occupational risk factors are one of the major causes of respiratory diseases and the cause accounts for 13% of all causes of COPD (11). Scientists have done a lot of researches on different types of work related to COPD. Shaikh *et al.* (11) made a cross sectional survey using a questionnaire among the brick kiln workers in Larkana and Dadu districts, Sindh, Pakistan. A total of 340 adult men were assessed using translated version of the American Thoracic Society Division of Lung Disease (ATS-DLD) questionnaire. They showed that 22.4% workers had chronic cough while 21.2% reported chronic phlegm, 13.8% had two or more attacks of shortness of breath with wheezing, 17.1% workers were suffering from Chronic Bronchitis. Amongst the non-smoking workers, 8.9% had chronic bronchitis. Multivariate analysis found that workers involved in brick baking were more likely to have chronic bronchitis (OR, 3.7; 95% CI: 1.1–11.6, P≤0.05) compared to those involved in carriage and placement work. Bala *et al.* (12) also reported a cross-sectional study of COPD in iron-steel and ferrochrome industry workers. Aim to assess the incidence and severity of COPD, the link between work-place air pollution and COPD, their conclusion was that the incidence of COPD was high and its severity of symptoms was severe in the study of large sample, and that there was a well correlation between work-place air pollution and COPD. Occupational air pollution not only increased the morbidity of workers' lung disease, but also may affected surrounding residents. Liu *et al.* (13) researched the relationship between residential proximity to fuel-fired powered plants and hospitalization rate for respiratory diseases. Rates of hospitalization for asthma, acute respiratory infection (ARI), and COPD were estimated using hospitalization data for 1993–2008 from New York State. After adjusting according to age, sex, race, median household income, and rural/urban residence, there was a significant 17% increases in estimated rates of hospitalization for COPD, among individuals >10 years of age living in a ZIP code containing a fuel-fired powered plants compared with other people who lived in area where there was no fuel-fired powered plants. They summarized that exposure to air pollution from fuel-fired powered plants and volatile compounds coming from hazardous waste sites increased the risk of hospitalization for respiratory diseases.

In addition to human activities, spontaneous disaster can also cause air pollution, subsequently results in happening of COPD. Tam *et al.* (14) assessed any associations between dust storms and emergency hospital admissions due to respiratory disease in Hong Kong. The data on daily emergency admissions for respiratory diseases to major hospitals in Hong Kong, and indices of air pollutants and meteorological variables from January 1998 to December 2002 were obtained from several governmental departments. They identified five dust storm days during the study period. The result of the study was that significant increases in emergency hospital admission due to COPD were found 2 days after dust storm episode. The relative risk of PM10 for lag 2 days was 1.05 (95% CI: 1.01–1.09) per 10 μg/m^3. They summarized that dust storms had an adverse effect on emergency hospital admission for COPD in Hong Kong, and suggested the adverse effect of coarse particles on lung health.

Scientists not only studied various causes formed pollutional haze, but also researched the effects of particle haze on COPD. Such as, PM2.5, PM10, SO_2, NO_X, O_3, etc. A hybrid approach was proposed to estimate exposure degree to fine particulate matter (PM2.5) at a given location and time. This approach was built on satellite-based aerosol optical depth (AOD), air pollution data from sparsely distributed Environmental Protection Agency (EPA) sites and local time-space Kriging, which was an optimal interpolation technique. Kumar *et al.* (15) developed an empirical relationship between the 2 km AOD and PM2.5 data from EPA sites. In the epidemiological application of the hybrid approach, admissions for an acute exacerbation of chronic obstructive pulmonary disease (AECOPD) was examined with respect to time-space lagged PM2.5 exposure. Their analysis suggested that the risk of AECOPD increased 2.3% with a unit increase in PM2.5 exposure within 9 days and about 5 km distance lags. Hansel *et al.* (16) came to conclusion that indoor pollutant exposure, including PM2.5 and NO_2, was associated with increased respiratory symptoms and risk of COPD exacerbation by means of a cohort study. The conclusion, which higher levels of PM2.5 may increase the risk of admissions for COPD, was also demonstrated by Tsai *et al.* (17).

With respect to an increase of 10 μg/m^3 in PM10, Faustini *et al.* (18) found a 0.67% increase for COPD hospitalization. The paper of effects of bushfire smoke on daily mortality and hospital admissions in Sydney, Australia (8) also indicated that a 10 mg/m^3 increase in bushfire PM10 was associated with a 3.80% (1.40% to 6.26%) increase in COPD hospitalization (at lag 2). In a study, the results of the Italian EpiAir Project were reported on the effect of air pollution on hospital admissions in 9 Italian cities during 2001–2005. The relationship between PM10, gases (NO_2 and O_3) and hospital admissions for cardiac disease, cerebrovascular disease, respiratory disease, pulmonary embolism and diabetes has been evaluated. Colais *et al.* (19) found that the association between air pollutants and hospitalization for respiratory diseases (respiratory infections, COPD and asthma) and showed different lags for the three pollutants: the effect of PM10 was immediate at lag 0–1 while the effects of NO_2 and O_3 were prolonged at lag 0–5. Cirera *et al.* (20) studied the short-term effects of major air pollutants and aeroallergen pollen on asthma and COPD hospital emergency room (ER) visits in the industrial and Mediterranean Spanish city of Cartagena during 1995–1998. Finally, they found that air levels of SO_2 and NO_2 were associated with a substantial increased risk in ER visits due to asthma and COPD. Stieb *et al.* (21) showed O_3 (lag 2 days) was most consistently associated with respiratory visits [3.2% (95% CI: 0.3–6.2%), and 3.7% (95% CI: –0.5–7.9%) increases in COPD visits per 18.4 ppb]. Carbon monoxide (CO) (OR, 1.19) showed a significant association for COPD exacerbations, Santus *et al.* (22) covered.

Surprisingly, Smit *et al.* (23) studied the relationship between air pollution from livestock farms and asthma, allergic rhinitis and COPD among neighboring residents and revealed PM10 emission was inversely correlated to asthma, allergic rhinitis and COPD ($P<0.05$). The final conclusion was that air pollution from livestock farms were inversely correlated to respiratory morbidity among neighboring residents. The verdict was very interesting and unpredictable, further research was required.

Pathogenesis and pathology of COPD induced by haze

The researchers have published many papers on COPD pathogenesis and pathological changes, but the papers on pathogenesis and pathological changes of COPD related to pollutional haze are not much. Here we'll focus on the pathogenesis and pathological changes of COPD caused by pollutional haze.

Bronchial epithelial cells of degeneration, necrosis, shedding can be seen in the airway of COPD patients. Studies about epithelial cells changes in COPD patients are concluded as follows: cigarette smoke and smoking-induced inflammation decrease cystic fibrosis transmembrane conductance regulator (CFTR) activity and mucociliary transport in the nasal airway and cultured bronchial epithelial cells. Sloane *et al.* (24) compared lower airway CFTR activity in current and former smokers with COPD, current smokers without COPD, and lifelong nonsmokers in order to explore the relationships between clinical characteristics and CFTR expression and function and found that smokers with and without COPD have reduced lower airway CFTR activity compared with healthy nonsmokers, and this finding correlates with disease phenotype. Acquired CFTR dysfunction may contribute to COPD pathogenesis. Maybe not only smoking can lead to acquired CFTR dysfunction, but also particle haze can lead to acquired CFTR dysfunction. Normal bronchial epithelial cell are connected to each other by cell adhesion molecules, so when these adhesion molecules are absent, which will inevitably lead to epithelial cell separated and shed. Kratzer

et al. (25) studied the role of endothelial cell adhesion molecule CD146 in the pathogenesis of COPD. They showed that CD146 expression was significantly decreased in the lung tissue of smokers with COPD and also in rats exposed to second-hand smoke (SHS). The results indicated that loss of CD146 function damaged pulmonary endothelial integrity. There are also some discoveries that cell adhesion molecules change may play a key role in the pathogenesis of COPD caused by pollutional haze. Li *et al.* (26) found a phenomenon which is Ca2+ influx into human airway epithelia elicited by diesel exhaust particles (DEP). They determined that human respiratory epithelial (HRE) cells possess proteolytic signaling ability, whereby proteinase-activated receptor-2 (PAR-2) activates Ca2± permeable TRPV4, which leads to activation of matrix metalloproteinase-1 (MMP-1), a signaling cascade initiated by DEP, a globally relevant air pollutant. Moreover, they observed expression of PAR-2, TRPV4, and phospholipase-Cβ3 in human airway epithelia and their DEP-enhanced protein-protein complex formation. The predisposed TRPV4P19S variant enhanced Ca2+ influx and MMP 1 activation. These results provided linkage between man-made air pollution and human airway disease.

COPD involves aberrant airway inflammatory responses to cigarette smoke (CS) that are associated with epithelial cell dysfunction, cilia shortening, and mucociliary clearing capacity. Lam *et al.* (27) identified cytosolic histone deacetylase 6-mediated (HDAC6) as a critical regulator of autophagy-mediated cilia shortening during CS exposure. Mice bearing an X chromosome deletion of Hdac6 (Hdac6-/Y) and MTECs had been reduced autophagy and were protected from CS-induced cilia shortening. Patients with COPD have a variety of bronchial wall infiltration of inflammatory cells, neutrophils, lymphocytes, NK cells, macrophages and monocytes. Airway inflammation is associated with cell factors, pulmonary vascular and other mechanism. van der Toorn *et al.* (28) verified the critical role of aldehydes in cigarette smoke-induced acute airway inflammation. They demonstrated that aldehydes present in CS played a critical role in inflammatory cytokine production and neutrophilic but not mononuclear airway inflammation. Meng *et al.* (29) evaluated the changes of CD[4](+)IL-17(+) T (Th17) and CD[4](+) Foxp3(+) regulatory T (Treg) cells in peripheral blood and bronchoalveolar lavage fluid (BALF), and therefore to explore the role of Th17 and Treg cells in cigarette smoke-induced airway inflammation in COPD rats. The results of the study showed that IL-17, IL-6, and ratio of Th17, the level of IL-17 mRNA was higher in the 12 wk and the 24 wk smoke-exposure groups in peripheral blood and BALF than that in the12 wk and the 24 wk control group. Ratio of Treg cells in BALF was higher in the smoke-exposure groups compared with the control groups. Th17 in smoke-exposure groups was positively correlated with counts of total cells and macrophages (r=0.512, 0.543, all P<0.05). While, Wang *et al.* (30) investigated the ratio of Th17/Treg cells in mice with chronic cigarette smoke exposure. They found that mice with chronic CS exposure showed significant increase in lung Th17 counting. Meanwhile, there was obvious decrease in Treg cell counting. Similar tendency was also found for the Th17/Treg cell ratio in peripheral blood. Further research on regulation of Th17/Treg cell balance are needed. About T cells studies are not limited in smoking COPD. Van Voorhis *et al.* (31) determined whether exposure to PM could impact Th17 polarization in an AHR-dependent manner. They used both cell culture techniques and *in vivo* exposure in mice to examine the response of T cells to PM. Initially experiments were conducted with urban dust particles from a standard reference material, and ultimately repeated with freshly collected samples of diesel exhaust and cigarette smoke. They finally identified a novel mechanism whereby PM could directly act on the AHR in T cells, leading to enhanced Th17 differentiation. Wortham *et al.* (32) indicated that NKG2D stimulation during long-term CS exposure is a central pathway in the development of NK cell hyperresponsiveness in COPD. Chaudhuri *et al.* (33) demonstrated DEP exposure *in vitro* alters monocyte differentiation and function. They reported that chronic diesel exhaust particle exposure may therefore altered both numbers and function of lung macrophages differentiating from locally recruited monocytes in the lungs of healthy people and patients with COPD.

Oxidative stress is basic mechanism of inflammation, many scientists researched oxidative stress reaction induced by pollutional haze elements. Particulate matters (PM) produce adverse effects on the respiratory system and cause COPD. Torres-Ramos *et al.* (34) studied the effect of PM2.5 in red blood cell (RBC) membranes from healthy volunteers (n=11) and COPD patients (n=43). They concluded that PM2.5 increased damage to RBCs of COPD patients, decreased the activity of phospho-tyrosine phosphatase (PTPase) and glucose 6 phosphate dehydrogenase (G6PD), and altered the function of the anionic exchanger (AE1) and the antioxidant response by decreasing SH groups. Later, they further investigated the activities of enzymes in RBCs that were related to glutathione metabolism

under conditions of increasing oxidative stress, which were associated with COPD progression, by increasing cellular damage *in vitro* with PM2.5, a ROS generator. The results showed significant decreases in the oxidation of the G6PD, glutathione peroxidase (GPx), and glutathione reductase (GR) proteins, which resulted in decreased enzymatic activity. By contrast, an increase ($P<0.05$) in the activity of glyceraldehyde 3 phosphate dehydrogenase (GAPDH) was observed, suggesting a pool of ATP on the membrane (35). Ultrafine particles or nanoparticles (UFPs or PM0.1) are able to inhibit phagocytosis, and to stimulate inflammatory responses, to damage epithelial cells and potentially to gain access to the interstitium. Terzano *et al.* (36) reported that chronic exposure to UFPs could produce deleterious effects on the lung, also causing oxidative stress and enhancing pro-inflammatory effects in airways of COPD patients. Kurmi *et al*. (37) aimed to characterize the oxidative potential (OP) of PM collected during the burning of wood and mixed biomass, whilst cooking food in the Kathmandu Valley, Nepal. They showed that incubation of mixed biomass and wood smoke particles suspensions with the synthetic respiratory tract lining fluid (RTLF) for 4 h resulted in a mean loss of ascorbate of 64.76%±16.83% and 83.37%±14.12% at 50 μg/mL, respectively. Reduced glutathione was depleted by 49.29%±15.22% in mixed biomass and 65.33%±13.01% in wood smoke particles under the same conditions. In addition, transient receptor potential channels ankyrin 1 (TRPA1), which was gated by oxidative and nitrosative stress by products, had been found to mediate inflammatory responses produced by an unprecedented series of toxic and irritant agents produced by air pollution, contained in cigarette smoke, and produced by accidental events at the workplace, which was found by Smit *et al.* (38).

With respect to COPD, ASM cells commonly occur fracture, atrophy. Some scientists studied about the pathophysiological abnormalities of airway smooth muscle. Xie *et al.* (39) revealed the function of heat shock protein 70 (Hsp70) in ASM of COPD patients. They demonstrated that one-month exposure of rats to cigarette smoke/air mixture led to increased expression of Hsp70 and heat shock transcription factor (Hsf1) in ASM compared with controls, whereas 3-month exposure caused dramatically reduced Hsp70 and Hsf1 compared with control animals. In addition, 3-month exposure to cigarette smoke/air mixture resulted in significantly lower Hsp70 and Hsf1 in rats ASM than 1-month exposure ($P<0.001$), and it was a positive correlation of Hsf1 and Hsp70. Finally, they summarized that long-term cigarette smoking results in reduced expression of Hsp70 in ASM. The change of Hsp70 in ASM maybe occurs under haze related COPD. Smelter *et al.* (40) examined Thymic stromal lymphopoietin (TSLP) and the TSLP receptor (TSLP-R) expression and function in human ASM cells under normal conditions and following exposure to cigarette smoke extract (CSE). Western blot analysis of human ASM cells showed significant expression of TSLP and TSLP-R, with increased expression of both by overnight exposure to 1% or 2% CSE. Furthermore, CSE increased TSLP release by ASM. Overall, these novel data suggest that cigarette smoke, TSLP, and ASM are functionally linked and that cigarette smoke-induced increase in airway contractility may be mediated via ASM-derived increases in TSLP signaling. The investigation of pathogenesis and pathology of ASM cell on COPD related to pollutional haze is asked to further discussed.

Accompanied by the degeneration, necrosis, and shedding of bronchial epithelial cells, shortening of the ciliated cells, bronchial wall inflammation, and bronchial smooth muscle damage, hyperplasia happened around submucosal and bronchial fibrous tissue due to inflammation related to pollutional haze, bronchial wall's damage and repair process repeated, leading to airway remodeling, bronchial stenosis, airflow limitation, further developing into obstructive pulmonary emphysema. Pentoxifylline (PTX) mediated transformation of pulmonary emphysema into pulmonary fibrosis under chronic cigarette smoke exposure, which was associated with upregulation of β-catenin and elevation of TGF-β_1, implying that activation of Wnt/β-catenin signaling may be involved in the pathogenesis of pulmonary fibrosis. The conclusion was obtained through the study on Male BALB/c mice by Wang *et al.* (41) and Glynos *et al.* (42) discussed the role of soluble guanylyl cyclase (sGC) in COPD, they found that pulmonary expression of sGC, both at mRNA and protein level, was decreased in smokers without airflow limitation and in patients with COPD, and correlated with disease severity (FEV_1%). Rokadia *et al.* (43) used pooled cross-sectional data from the National Health and Nutrition Examination Survey 1999–2002 to evaluate the association between cystatin C (CysC) and emphysema. They showed that the mean (SE) CysC level in the emphysema group was significantly higher than that in normal controls {1,139 [22] *vs.* 883 [8] μg/L; $P=0.001$}. Active smokers with emphysema had 115.4 (46.5) μg/L higher mean (SE) CysC levels than the normal controls ($P<0.001$). Upon adjusted analysis, they observed that nonactive smokers with significant ETS

exposure had 31.2 (15.2) μg/L higher mean (SE) serum CysC levels as compared to ETS unexposed nonactive smokers (P=0.04). Overall, these findings suggested that CysC may play a role in the pathogenesis of smoking-related emphysema. Above studies are about the mechanism of cigarette related COPD. Pulmonary fibrosis, airflow limitation and emphysema of COPD related to haze remains to be studied.

Alpha-1-antitrypsin deficiency (AATD) is one of the mechanisms of COPD, especially in Europe and the United States race. Decline of FEV_1 and diffusion capacity for carbon monoxide per liter of alveolar volume (KCO) in subjects of the PiZZ genotype from the UK AATD registry were studied by Pauwels *et al.* (44). They observed that high PM10 exposure predicted more rapid decline of FEV_1 (P=0.024). In a similar analysis for KCO decline, higher baseline KCO predicted rapid decline (P<0.001) as did higher exposure to O_3 (P=0.018). High PM10 exposure also showed a trend towards this effect (P=0.056). In conclusion, exposure to O_3 and PM10 predicts decline of lung function in AATD.

Temperature inversions result in the accumulation of air pollution, often to levels exceeding air quality criteria, and contribute to the progress of COPD. Wallace *et al.* (45) investigated the effect of boundary layer temperature inversions on sputum cell counts. Total and differential cell counts of neutrophils, eosinophils, macrophages and lymphocytes were quantified in sputum samples of patients attending an outpatient clinic. Temperature inversions were identified using data from the Atmospheric Infrared Sounder. On inversion days, a statistically significant increase in the percent of neutrophils was observed in stable patients. There was also a statistically significant increase in the percent of macrophages in exacerbated patients. In the stable and exacerbated groups, percentage of neutrophils and macrophages increased by 12.6% and 2.5%, respectively. They found that monthly averages of total cell counts were strongly correlated with monthly NO_2 concentrations, which was not previously identified in the literature.

Biological markers of COPD related to pollutional haze

Biochemical markers can be used as monitoring indexes of COPD so as to further understand the progression of COPD. Kelly *et al.* (46) surveyed baseline level of some PM_X in London area and found that PM10, which increased oxidative activity, appeared to be associated with increased concentrations of copper (Cu), barium (Ba), and bathophenanthroline disulfonate-mobilized iron (BPS Fe) in the roadside samples. As for PM2.5, no simple association could be seen. So we could monitor Cu, Ba, and BPS Fe as PM10 oxidative activity. Dadvand *et al.* (47) studied the relevant content of air pollution, biomarkers of systemic inflammation and tissue repair in COPD patients. The results told us that an IQR increase in NO_2 exposure in lag 5 was 51%, 10% and 9% in CRP, fibrinogen and HGF levels, respectively. They also observed 12% and 8% increases in IL-8 associated with an IQR increase in NO_2 exposure in lag 3 and over the year before sampling, respectively. These increases were larger than that in former smokers. The study results for PM2.5 were not found consistent results. Canova *et al.* (48) made a bidirectional, hospital-based, case-crossover study, 209 patients admitted for asthma or COPD to the Chelsea and Westminster Hospital (London), with 234 admissions, were recruited between May 2008 and July 2010. PM10 levels in the area of Kensington and Chelsea at the time of admission were compared with the levels 14 days before and 14 days after the event. Conditional logistic regression was used to estimate the effect of PM10 at several temporal lags, while controlling for confounders. They reported that serum vitamin C modified the effect of PM10 on asthma/COPD exacerbations. A similar (although weaker) influence was observed for low levels of uric acid and vitamin E, whereas vitamin A showed no effect modification. Their study suggested that the concentration of antioxidants in patients' serum modified the short-term effects of PM10 on asthma and COPD exacerbations, consequently, we can know the degree of COPD exacerbation by PM10 through monitoring serum vitamin C, low levels of uric acid and vitamin E.

In addition to monitoring the blood index, respiratory sediment parameters can also directly reflect the severity degree of respiratory disease. Löndahl *et al.* (49) determined respiratory tract deposition of diesel combustion particles in patients with COPD during spontaneous breathing. They observed that the deposited dose rate increased with increasing severity of the disease. However, the deposition probability of the ultrafine combustion particles (<100 nm) was decreased in COPD patients. Also reported that the higher deposited dose rate of inhaled air pollution particles in COPD patients might be one of the factors contributing to their increased vulnerability. The strong correlations between lung function and particle deposition, especially

in the size range of 20–30 nm, suggested that particle deposition could be used as an indicator of respiratory disease. Therefore, we can evaluate COPD through measuring respiratory tract particle deposition.

Therapy of haze related COPD

In addition to conventional anti-inflammatory therapy, scientists also have studied the special treatments or measures about haze related COPD. Now described as follows:

The most effective measure of COPD related to haze should be to bear the brunt of controlling the haze. Schikowski *et al.* (50) completed a clinical research whether different declines in air pollution levels in industrialized and rural areas in Germany were associated with changes in respiratory health over a period of about 20 years. They used data from the SALIA cohort study in Germany (study on the influence of air pollution on lung function, inflammation and aging) to assess the association between the incidence and severity degree of COPD and the decline in air pollution exposure. They found when ambient air concentrations of PM10 declined in average by 20 mg/m^3, the incidence of chronic cough with sputum production and mild COPD at baseline investigation decreased compared to follow-up was 9.5% *vs.* 13.3% and 8.6% *vs.* 18.2%, respectively. A steeper decline of PM10 was observed in the industrialized areas in comparison to the rural area, this was associated with a weaker increase in attacks of COPD. Similarly, Dockery *et al.* (51) surveyed effect of air pollution control on mortality and hospital admissions in Ireland. They explored and compared the effectiveness of the sequential 1990, 1995, and 1998 bans, which Irish government introduced on the marketing, sale, and distribution of coal, in reducing community air pollution and in improving public health. They reported that mean black smoke (BS) concentrations fell in all affected population centers post-ban compared with the pre-ban period, with decreases ranging from 4 to 35 mg/m^3 (corresponding to reductions of 45% to 70%, respectively), but they didn't observe the same change in SO_2 concentration as total gaseous acidity associated with the bans. In comparison with the pre-ban periods, respiratory disease mortality was reduced, admissions to hospitals for COPD were reduced. Controlling the air quality, which requires the joint efforts of international organizations, governments and people in the world, can effectively prevent the occurrence of COPD. Of course, discussion and further research are needed to develop the effect of air quality control measures on COPD and how to improve air quality.

With the progress of COPD related to haze, hypoxemia, polycythemia, pulmonary heart disease and congestive heart failure and other complications occurred. Therefore, it is not enough only to control acute exacerbation for treatment of COPD related to haze and better measures should be pursued through unremitting efforts to gradually reduce symptoms and improve quality of life. So, the following comprehensive measures should be considered: health education, psychological and drug therapy, oxygen therapy and aerosol inhalation treatment, physical therapy, respiratory and systemic exercise and nutrition support and so on. Miyamoto *et al.* (52) testified that pulmonary rehabilitation improves exercise capacity and dyspnea in air pollution-related respiratory disease. Subjects were enrolled in a 12-week (2-week inpatient followed by 10-week outpatient) pulmonary rehabilitation program. The program comprised conditioning, strength training, endurance training, and patient education. Twenty-nine subjects (mean age 74.2±10.1 years, 11 males) completed the program, including 11 subjects with COPD and 18 subjects with asthma. Following rehabilitation, the participants (n=29) showed significant improvements in MMRC dyspnea grade, vital capacity % predicted, quadriceps force and ISWD (all $P<0.05$). Subjects with COPD showed significant improvements in quadriceps force and ISWD (both $P<0.05$). Diaz-Guzman *et al.* (53) stated that pulmonary rehabilitation must be considered regardless of the age of the COPD patient.

Suppressing key signal pathway associated with pathogenesis may be a new therapeutic approach for the treatment of haze related COPD. Transient receptor potential channels related to occupational exposure was reported by Smit *et al.* (38). One of their conclusions was that antagonists for TRP channels may be novel therapeutic options for the treatment of COPD related to haze. van Voorhis *et al.* (31) concluded that PM can directly act on the AHR in T cells, leading to enhanced Th17 differentiation. Further understanding of the molecular mechanisms responsible for pathologic Th17 differentiation and autoimmunity reaction after exposure to pollution will allow direct targeting at proteins involved in AHR activation and function for treatment of PM exposures. There are also some experiments to study specific inhibitors in the control of COPD in recent years. Whether specific inhibitor of T cell responses represents a therapeutic strategy? Podolin

et al. (54) demonstrated that therapeutic inhibition of T cell responses may be efficacious in the treatment of COPD. Zhang *et al.* (55) explored the protective effects of anti-TNF-α antibody, infliximab, in the development of emphysema induced by passive smoking in rats. They came to conclusion that Infliximab protected against cigarette smoking-induced emphysema by reducing airway inflammation, attenuating alveolar septa cell apoptosis and improving pathological changes. Maybe this antibody can control the progress of COPD in clinical practice.

Concluding remarks

In spite of achievements made during the last several years, there are still some weak areas need to be further researched. (I) There is lack of large scale studies on the pathogenesis and pathological changes of COPD induced by haze; (II) although there are a lot of papers about COPD biological markers, only a few indicators are associated with haze; (III) most researches are focus on haze effect on bronchial epithelial cells, smooth muscle cells, but lacking of effect of haze on airway secretions, and effects of these haze particles on bronchial goblet cells and mucous cells; (IV) study on treatment of haze related COPD is not much, and little research has focused on personalized therapy considering factors from genetic to environment impacts for each individual; (V) there is a need for study on special drug therapy on COPD induced by pollutional haze.

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Footnote

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