NSFC spurs significant basic research progress of respiratory medicine in China

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Abstract

Over the years, research in respiratory medicine has progressed rapidly in China. This commentary narrates the role of the National Natural Science Foundation of China (NSFC) in supporting the basic research of respiratory medicine, summarizes the major progress of respiratory medicine in China, and addresses the main future research directions sponsored by the NSFC.

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Authorship and contributorship

Ruijuan Sun and Feng Xu designed and drafted the manuscript; Feng Xu collected and analyzed data; Erdan Dong and Chen Wang revised the manuscript and outlined its structure. The manuscript has been read and approved by all coauthors.

Ethics

This study is in accordance with the Author Guidelines.

Conflicts of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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Introduction

Respiratory diseases seriously affect the health of the Chinese population. With the economic development and environmental deterioration because of industrialization in China, respiratory diseases cause 10.56% and 13.31% of mortality in rural and urban China, respectively, (ranking number 3 and 4 among the leading causes of death) (1).

As the largest grant funding agency for basic research in China, National Natural Science Foundation of China (NSFC), which was established in 1986, dramatically spurs vigorous advances in respiratory medicine to understand and treat diseases. The Department of Health Sciences (DHS) at the NSFC gives priority to basic research about the causes, diagnosis, prevention and cure of human diseases and the application of that knowledge to enhance human health of the nation. The objective of DHS is to facilitate the development of health sciences in China. Within DHS, the Division of Respiratory Diseases (DRD) is responsible for supporting basic research in diverse respiratory diseases with the exception of respiratory malignancies. Areas of research supported include bronchial asthma, Chronic Obstructive Pulmonary Disease (COPD), interstitial lung diseases, acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), pulmonary hypertension (PH), pulmonary embolism, respiratory failure, sleep disordered breathing, lung transplantation and protection.

NSFC promotes persistent basic research progress of respiratory medicine in China

Over the years, NSFC has given comprehensive, long-term, multi-levels and large-scale funding to relevant researches in respiratory diseases. The number of funded projects and the amount of grants in respiratory medicine are shown in Figs. 1 and 2, respectively. Funding has rapidly increased since 2001, especially after 2009. The detailed supporting information from 18 different DRD-funded research areas (coded as H0101–H0118) is listed in Figs. 3 and 4. Under the sponsorship of the NSFC in the past 26 years, a dozen of active research groups have obtained significant achievements in the diverse areas of respiratory medicine. Major and important work by researchers of China is reviewed below.

Respiratory infections

China has made great contributions to the control of pulmonary infections, in particular concerning a couple of new pulmonary viral diseases, causative of a
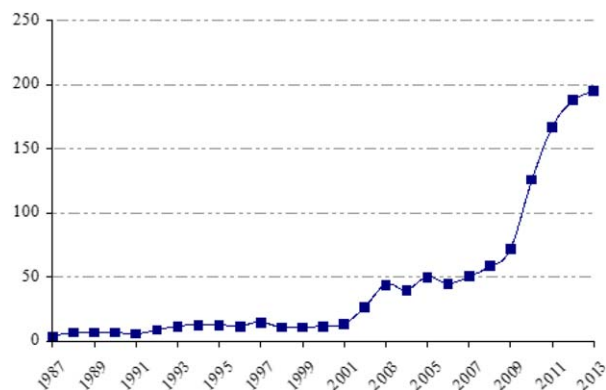

Figure 1. The number of NSFC-funded projects in respiratory medicine from NSFC (1987–2013).

pandemic, great financial loss and social panic. In the year 2003, Nanshan Zhong (Guangzhou Medical College) and other researchers isolated severe acute respiratory syndrome (SARS) coronavirus (CoV) in Guangdong. They demonstrated SARS CoV was responsible for the epidemic outbreak and the prototypical SARS-CoV strain found in other countries (2). Zhong also proposed corticosteroid treatment for critical SARS and confirmed proper corticosteroid use decreased mortality and hospital stay, and was not significantly associated with secondary lower respiratory infection or other severe complications (3, 4). Further studies revealed detectable persistence of IgG antibodies and neutralizing viral antibodies for up to 720 days. (5). In a rhesus macaque model, potent siRNA inhibitors of SARS-CoV provided relief from fever, diminished viral levels and reduced acute diffuse alveoli damage (6). The group of Chengyu Jiang (Chinese Academy of Medical Sciences, CAMS) reported the entry of SARS-CoV into cells was mediated by a heparin sulfate proteoglycans-mediated, but clathrin- and caveolae-independent mechanism (7, 8). Zhengli Shi
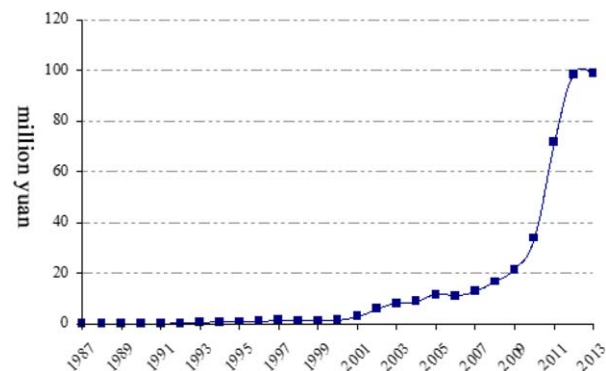

Figure 2. The amount of NSFC funding in respiratory medicine from NSFC (1987–2013).
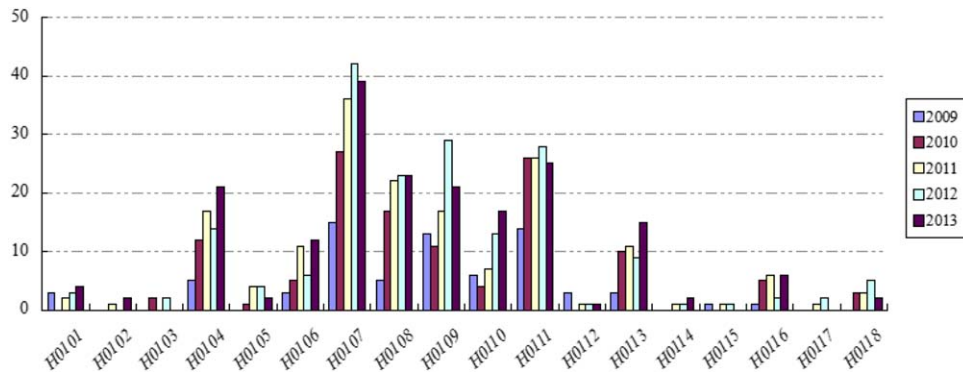
Figure 3. The number of funded grants from DRD, 2009–2013. Abbreviations: H0101, Structure, function and development of lung and airway; H0102, Hereditary respiratory diseases; H0103, Dysfunction of respiratory modulation; H0104, Respiratory inflammation and infection; H0105, Respiratory immunological and allergic diseases; H0106, Airway remodeling and diseases; H0107, Bronchial asthma; H0108, Chronic Obstructive Pulmonary Disease (COPD); H0109, Pulmonary circulation and vascular diseases; H0110, Interstitial lung diseases; H0111, Acute lung injury/ARDS; H0112, Respiratory failure and mechanic support; H0113, Sleep-disordered breathing; H0114, Mediastinum and pleural diseases; H0115, Structure, function and development of thoracic cage and diaphragm; H0116, Lung transplantation and protection; H0117, New technology of diagnosis and treatment in respiratory diseases; H0118, Other scientific issues in respiratory diseases.

(Chinese Academy of Sciences, CAS) and coworkers reported whole-genome sequences of two novel bat CoVs from Chinese horseshoe bats in Yunnan, China: RsSHC014 and Rs3367. These viruses were far more closely related to SARS-CoV than any previously identified bat CoVs, particularly in the receptor binding domain (RBD) of the spike protein. Most importantly, they found the first recorded isolation of a live SARS-like-CoV strain, with typical CoV morphology sharing 99.9% sequence identity to Rs3367, utilizing angiotensin-converting enzyme 2 from humans, civets and Chinese horseshoe bats for cellular entry. These results provide the strongest evidence that Chinese horseshoe bats are natural reservoirs of SARS-CoV (9). The newly emergent Middle East respiratory syndrome CoV (MERS-CoV) causes severe pulmonary disease in humans, representing the second example of a highly pathogenic CoV. Fu Gao (Chinese Center for Disease Control and Prevention, CCDC) delineated the specific

interaction between the free RBD of the MERS-CoV spike protein and CD26, the cellular receptor for MERS-CoV (10). Chuan Qin (CAMS) developed rhesus macaques as a model for MERS-CoV. The infected monkeys exhibited clinical signs of disease, viral replication, histological lesions and produced neutralizing antibody (11). Taijiao Jiang (CAS) developed a new computational method PREDAC, predicting antigenic clusters of H3N2 influenza virus with high accuracy from viral hemagglutinin (HA) sequences. The coupling of large-scale HA sequencing with PREDAC can significantly improve vaccine strain recommendation (12). Jiang's work provides an urgently needed tool for rapid and large-scale analysis of HA receptor specificities for global influenza surveillance. The group of Chengyu Jiang found autophagic cell death of alveolar epithelial cells plays a crucial role in the high mortality rate of H5N1 infection, and autophagy-blocking agents might be useful against H5N1-induced lung injury
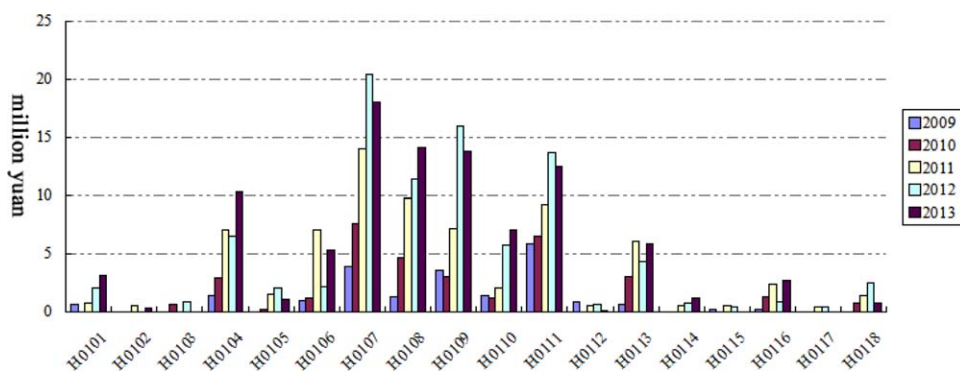

Figure 4. The amount of DRD-funded grants, 2009–2013.

(13). IL-17 Monoclonal antibodies were reported to be potential treatment agent for H1N1virus (14). Hongyan Wang (CAS) and coworkers first demonstrated that adhesion and degranulation-promoting adapter protein (ADAP) regulates the positive feedback loop of TGF-β1 production and TGF-β1-induced CD103 expression in CD8$^+$ T cells via the TβRI-TRAF6-TAK1-SMAD3 pathway and protects from influenza virus (i.e. H5N1 or H1N1) infection (15). Chen Wang (Capital Medical University) and coworkers reported oseltamivir and maxingshigan- yinqiaosan, alone and in combination, reduced time to fever resolution in H1N1 patients (16). During an influenza pandemic in mainland of China in 2013, Yuelong Shu (CCDC) and coworkers reported isolation of a novel re-assortment of avian-origin influenza A virus, identified as H7N9. Further sequencing analyses revealed, all gene segments from the virus were of avian origin (17). Lanjuan Li (Zhejiang University)'s team found a similar viral isolate from patients and epidemiologically linked market chickens. The H7 of the isolated viruses was closest to that of the H7N3 virus from domestic ducks in Zhejiang, whereas the N9 was closest to that of the wild bird H7N9 virus in South Korea. Gln226Leu and Gly186Val substitutions in human virus H7 and the PB2 Asp701Asn mutation were identified (18). Hualan Chen (Gansu Agricultural University) and coworkers systematically analyzed H7N9 viruses isolated from birds and humans. They determined viruses isolated from birds were nonpathogenic in chickens, ducks and mice, but viruses isolated from humans caused up to 30% body weight loss in mice. One virus isolated from humans was highly transmissible in ferrets by respiratory droplet (19). Chuan Qin also reported that H7N9 virus was capable of transmission between ferrets via low level respiratory droplets. Four mutations were further identified in the virus isolated from the contact ferret (20). Fu Gao had evaluated the viral HA receptor-binding properties of two human H7N9 isolates and found that SH-H7N9 HA preferentially binds the avian receptor analog, whereas AH-H7N9 HA binds both avian and human receptor analogs. Furthermore, an AH-H7N9 mutant HA (Leu226→Gln) exhibited dual receptor-binding properties, which indicated AH-H7N9 can bind human receptors while retaining avian receptor-binding properties (21). The prognosis of H7N9 infection is poor. Lanjuan Li and coworkers performed a comprehensive study to identify prognostic factors for H7N9, and found chronic heart disease was associated with increased hospitalization risk (22). The increased plasma levels of angiotensin II in H7N9 patients are associated with disease severity and mortality. Moreover, the predictive value of angiotensin II is greater than that of C-reactive protein, and some clinical parameters such asPaO$_2$/FiO$_2$ ratio (23). A national monitoring network in China for emergent infections, established after the SARS crisis in 2003, was crucial to timely prevention and treatment of the H7N9 infection.

The infection of bacteria is much more common among pulmonary infectious diseases. *Staphylococcus aureus* is one of the leading causes of severe pneumonia and sepsis. Macrophage polarization is critical for dictating host defense against pathogens and injurious agents. Feng Xu (Zhejiang University) found M1 macrophage skewing was regulated by PI3-K/Akt1-mediated miR-155/SOCS1 axis. Blocking of miR-155 in macrophages from Akt1$^{-/-}$ mice or knockdown of SOCS1 in cells from wild-type mice disabled or enabled, respectively, an M1 macrophage shift and antibacterial response (24). Guangwei Liu (Fudan University) indicated that the Akt1-STAT1 signaling axis negatively regulates neutrophil recruitment and activation in *S. aureus* infection in mice (25). These results implicate Akt1 as a promising target for the therapeutic intervention in *S. aureus* infection. Using a mouse model of secondary *Pseudomonas aeruginosa* pneumonia during sepsis-associated immunosuppression, Ju Cao (Chongqing Medical University) demonstrated IL-4 deficiency mice exhibited enhanced lung inflammation, neutrophil recruitment to airspaces and elevated pulmonary cytokine production, leading to impaired host defense (26). Similarly, IL-27 is also an important mediator of sepsis-induced impairment of pulmonary immune response upon *Pseudomonas aeruginosa* infection (27). Jieming Qu (Shanghai Jiao Tong University) found adipose tissue-derived mesenchymal stem cells (ASCs) exhibited protective effects on *P. aeruginosa* pulmonary infection by inhibiting production of prostaglandin E2, and improving phagocytosis and the bactericidal properties of macrophages. ASCs may provide a new strategy for pulmonary bacterial infections (28).

Fungal infection becomes more common, particularly among the elderly and immunocompromised people in China. Understanding of host-defense fundamental mechanisms may lead to the development of effective preventive and therapeutic strategies. Hui Xiao (CAS) found SHP-2 gene ablation in dendritic cells (DCs) and macrophages impaired the tyrosine kinase Syk-mediated signaling and abrogated pro-inflammatory response following fungal stimulation. SHP-2 facilitated the recruitment of Syk to the C-type lectin receptor (CLR) dectin-1 or the adaptor FcRγ, through its N-SH2 domain and a carboxy-terminal immunoreceptor tyrosine-based activation motif. DC-derived SHP-2 was crucial for anti-fungal responses of the TH17 cells in controlling infection with Candida

albicans. This study highlights the importance of the concerted actions of different CLRs on various cells of the innate immune system against fungi (29). Vitamin D plays an important role in pulmonary immunity, and its deficiency has been linked to various respiratory infections. Yi Shi (Nanjing University) identified that β-glucan, the major *Aspergillus fumigatus* cell wall component, as the major agent for upregulation of 1α-hydroxylase and vitamin D receptor, and vitamin D production in human bronchial epithelial cells. Upon *A. fumigatus* exposure, vitamin D deficiency led to higher mortality and greater fungal load, which was accompanied with enhanced and sustained expression of inflammatory cytokines (30). Jieming Qu demonstrated transient overexpression of IFN-γ could augment host defense against *Aspergillus* by upregulation of killing ability of alveolar macrophages and lung leucocytes (31).

Tuberculosis (TB) is a major health problem in china. According to the 2014 WHO report on tuberculosis, there were an estimated 980 thousands incident cases of TB in mainland of china. The host immune system plays an important role in the development and control of disease during tuberculosis infection. Haiying Liu (Peking Union Medical College) and her coworkers investigated the clinical significance and immunological role of Gab2 in Mycobacterium TB infection. They found Gab2 negatively correlated with the level of TB antigen-specific IFN-γ secretion, and down-regulation of Gab2 showed a protective function against TB (32). Cuihua Liu (CAS) found that MTB tyrosine phosphatase PtpA suppressed innate immunity dependent on pathways of the kinases Jnk and p38 and NF-κB by exploiting host ubiquitin. The host adaptor TAB3 mediated NF-κB signaling by sensing ubiquitin chains, and PtpA blocked this process by competitively binding the ubiquitin-interacting domain of TAB3. Therefore, targeting of ubiquitin-PtpA interaction could be a potential tuberculosis treatment (33). Baoxue Ge (Tongji University) identified Epstein-Barr virus-induced gene 3(EBI3) rs4740 polymorphism is closely associated with susceptibility to pulmonary TB and the elevation and enrichment of EBI3 in the lung may contribute to the exacerbation of mycobacterial infection (34). Mucosal-associated invariant T (MAIT) cells have been shown to play an important role in host defense against mycobacterial infection. Xiaoxing Cheng (309th Hospital) compared the functions of MAIT cells between patients with active TB and healthy control subjects. They found MAIT cells in patients with active TB exhibited elevated expression of programmed death-1 (PD-1), and blockade of PD-1 signaling resulted in a higher frequency of BCG-stimulated IFN-γ production in MAIT cells (35).

Drug-resistant TB is a serious clinical problem. Shenjie Tang (Capital Medical University) conducted a prospective, multicentre, randomized study to evaluate the efficacy, safety and tolerability of linezolid in patients with extensively drug-resistant TB in China. The treatment success rate in linezolid therapy group was reported to 69.7%, significantly higher than that in the control group (34.4%) (36).

ALI/ARDS

China makes substantial efforts to investigate the cellular and molecular mechanisms of ALI/ARDS during recent years (37). Chunxue Bai (Fudan University) identified both capillary and alveolar epithelium stress failure contributed to high altitude pulmonary edema, and keratinocyte growth factor-2 (KGF-2) pre-administration significantly reduced lung injury and improved survival (38, 39). Later, the protective efficacy of KGF had been further confirmed in a human lung injury model by others (40). Bai *et al.* also demonstrated Prdx6 deletion exacerbated lung injury induced by LPS (lipopolysaccharide) via reduced capability to clear H_2O_2 (41). Feng Xu (Zhejiang University) and Liyun Shi (Hangzhou Normal University) recently reported miR-127 modulates macrophage polarization and promotes LPS induced-lung inflammation and injury by activating the Bcl6-Dusp1-JNK pathway. MiR-127 is a potential molecular target for the treatment of ALI (42). Intrapleural administration of mesenchymal stem cells (MSC) markedly attenuates the severity of endotoxin-induced ALI. This effect is likely mediated by paracrine/endocrine repair mechanism of MSC, and not rather than cellular engraftment mechanisms (43). Recently, in addition to its direct antimicrobial effect, tylvalosin was reported to exhibit anti-inflammatory property and attenuates ALI through suppression of NF-κB activation (44).

Pulmonary fibrosis

Utilizing alveoli epithelia-specific Shp2-knockout mice, Yuehai Ke (Zhejiang University)'s group identified a novel role of Src homology phosphotyrosyl phosphatase 2 (Shp2) in surfactant homeostasis, which demonstrated Shp2 deregulation induces spontaneous pulmonary fibrosis with minimal inflammation (45). They further exhibited that disruption of Shp2 promoted the association of JAK1 with interleukin 4 (IL-4Ra), resulting in M2 skewing through enhancing IL-4-mediated JAK1/STAT6 activation (46). Statin use is associated with interstitial lung abnormalities among smokers with COPD. Gene studies suggest statins may influence the susceptibility to pulmonary fibrosis. Jinfu

Xu (Tongji University) revealed bleomycin-induced lung inflammation and fibrosis in mice via enhanced the NOD-like receptor family, pyrin domain containing 3 (NLRP3)-inflammasome activation (47). Lingsong Li (CAS) and coworkers found that bone marrow derived-MSCs (BMSCs) maybe involved in lung fibrosis. They demonstrated the underlying mechanism to be lysophosphatidic acid (LPA)-induced BMSC differentiation into myofibroblast and ECM secretion via LPA1 (lysophosphatidic acid type-1 receptor) (48). Qinhua Liu (Shandong University) demonstrated early endostatin administration alleviated fibrotic changes in bleomycin-induced pulmonary fibrosis by decreasing microvascular density, infiltrating inflammatory cells, and increasing alveolar type II cell apoptosis. The levels of TNF-α and TGF-β1 were decreased after endostatin treatment (49). Dexiang Xu (Anhui Medical University) delineated the protective mechanisms of melatonin in bleomycin-induced pulmonary fibrosis include inhibition of GRP78 up-regulation, elevation of the cleaved activating transcription factor-6 (ATF6) and activation of pulmonary elF2α. Melatonin also repressed pulmonary inositol requiring ER-to-nucleus signal kinase-1α (IRE1α) phosphorylation, consequently inhibiting activation of x-box binding protein-1(XBP-1) and JNK (50). Baofeng Yang (Harbin Medical University) identified the involvement of miR-26a in epithelial-mesenchymal transition (EMT) during idiopathic pulmonary fibrosis. Inhibition of miR-26a resulted in transformation of lung epithelial cells into myofibroblasts whereas forced expression of miR-26a alleviated transforming growth factors-β (TGF-β1)- and bleomycin-induced EMT (51).

COPD

Nanshan Zhong organized a large-population, spirometry-based, cross-sectional survey of COPD, and reported the overall prevalence of COPD in China to be 8.2% (men, 12.4%; women, 5.1%). The prevalence of COPD was significantly higher in rural residents, elderly patients, smokers, and in those with lower body mass index, less education, poor kitchen ventilation, occupational exposure to dust or biomass fuels, childhood pulmonary problems or family history of pulmonary diseases (52). Further studies demonstrated indoor pollutants from biomass fuels and Chinese water-pipe smoking are important risk factors for non-smoking women with COPD (53, 54). ChemR23 and tissue inhibitor of metalloproteinase-1 were identified as potential protein biomarkers of COPD (54). Zhong's team also revealed that carbocisteine, a mucolytic agent, reduced the yearly COPD exacerbation

(55). Cigarette smoke (CS) is a major risk factor for COPD development. Huahao Shen (Zhejiang University) demonstrated Tc17 cells, as an important source of IL-17A, were associated with CS-induced emphysema and deoxyribonucleic acid damage (56). Fuqiang Wen (Sichuan University) demonstrated astragaloside attenuated CS-induced airway inflammation via its anti-inflammatory and antioxidant properties, and sildenafil inhibited airway inflammation and mucus production via nitric oxide/cyclic guanosine 3′,5′-monophosphate pathway (57, 58). MSCs were reported to relieve airway inflammation and emphysema in CS-exposed rat models, through the inhibition of cyclooxygenase-2(COX-2)/prostaglandin E2 (PGE2) in alveolar macrophages (59). Ping Chen (Central-South University) demonstrated mitochondrial transcription factor (mtTFA) levels are associated with apoptosis of pulmonary vascular endothelial cells. Aberrant mtTFA methylation may play an important role in COPD pathogenesis (60). Jungang Xie (Huazhong University of Science and Technology) found IL-33 expression levels are increased in COPD patients and related to airway and systemic inflammation (61). Recently, Jiachun Lu (Guangzhou Medical University) demonstrated that functional germline variant c.353T>C (p.Val118Ala) of Snai1 confers consistently decreased risks of lung cancer and COPD (62).

Asthma

Asthma is characterized by airway inflammation, tissue injury/remodeling, bronchoconstriction and mucus hypersecretion. Nanshan Zhong and coworkers, in a cross-sectional national survey of 6304 patients, demonstrated house dust mites were the most prevalent allergens in patients with asthma and/or rhinitis in China. There were significant differences in sensitization pattern in patients from different geographical areas and age groups (63). Zhong *et al.* also demonstrated that the combination of cumulative dose for Leukotriene D(4) and potency ratio might be useful in identifying leukotriene-responsive asthmatic patients. Leukotriene D(4) and methacholine bronchial provocation tests are measurements of airway responsiveness (64). One year treatment with Alutard SQ house dust mite immunotherapy significantly reduced symptoms and medication use in patients with mild to moderate allergic asthma (65). Recently, Jia Yin (Peking Union Medical College) reported 12 months of daily treatment with sublingual mite allergen (mixture of Dermatophagoides pteronyssinus and Dermatophagoides farinae extracts) was well tolerated and effectively controlled disease in patients with moderate (but not

mild) persistent asthma (66). Huanzhong Shi (Capital Medical University) provided direct evidence that IL-4 and IL-5 increase airway responsiveness and airway infiltration of activated eosinophils in patients with allergic bronchial asthma (67, 68). Serum concentrations of both sCD86 and sCTLA-4 increased after allergen inhalation in sensitized asthmatic subjects, with levels correlating to asthma severity (69–72). Eosinophils not only act as terminal effector cells, but also actively modulate immune responses by promoting expansion of Th2 cells (73). Huahao Shen's team reported treatment with anti-CCR3 or dexamethasone can inhibit migration and differentiation of CD34$^+$ progenitor cells by regulating the eotaxin/CCR3 axis in asthmatic mice, demonstrating a novel molecular mechanism for the migration and *in situ* differentiation of CD34$^+$ progenitors (74). Exogenous IL-17 was shown to protect against allergic asthma, likely through inhibition of eosinophil differentiation in bone marrow (75). Their following work demonstrated airway epithelial protein tyrosine phosphatase SHP2 modulated TGF-β1 activities, leading to airway remodeling and lung dysfunction (76). Changchong Li (Wenzhou Medical College) demonstrated PI3K and Notch signal pathways coordinately regulate activation and proliferation of T lymphocytes in asthma by up-regulating cyclinD1 and down-regulating p27kip1 of CD4$^+$ T lymphocytes (77). Guanghong Tan (Hainan Medical College) verified Ag43/Fcε3, as a protein vaccine, produced neutralizing auto-antibodies to IgE, induced significant anti-asthma effects, and regulated IgE and Th cytokines in a murine asthma model (78). Rui He (Fudan University) showed chemerin attenuated allergic airway inflammation and hyperreactivity by suppressing airway recruitment of CD11c$^+$ CD11b$^+$ DCs via inhibition of CCL2 secretion by active lung epithelial cells (79). Guohua Zhen (Huazhong University of Science and Technology) found asthma patients with high epithelial expression of IL-25 had greater airway hyperresponsiveness, more airway and blood eosinophils, higher serum IgE, more subepithelial thickening and higher expression of Th2 signature genes. These patients responded well to inhaled corticosteroid treatment compared to IL-25-low patients (80).

Pulmonary hypertension

Zhicheng Jing (Tongji University) and coworkers reported the baseline characteristics and survival rates of Chinese patients with idiopathic and familial PH. After mean follow up of 40.1 months, the survival rates at 1, 2, 3 and 5 years were 68.0%, 56.9%, 38.9% and 20.8%, respectively. This study raises international concern about PH-related social burden in developing countries (81, 82). Through two prospective, open-label, multicenter clinical studies, ZhiCheng Jing reported the safety and efficacy oral sildenafil in Chinese patients with PH and Eisenmenger syndrome (83). He also participated in the registry study about the clinical features and prognosis of pediatric pulmonary hypertension, a part of the Pediatric Pulmonary Hypertension registry (84), and proposed the QRS duration and serum high-density lipoprotein levels might serve as an indicator of disease severity and prognosis in idiopathic PH patients (85, 86). Jian Wang (Guangzhou Medical College) and coworkers demonstrated sildenafil inhibits PH by reducing canonical transient receptor potential (TRPC) protein expression and intracellular calcium concentration. Sildenafil inhibits hypoxia-induced TRPC expression in pulmonary arterial smooth muscle via the cGMP-PKG-PPARγ axis (87, 88). Wang first demonstrated that there are expressions of TRPC, transient receptor potential vanilloid (TRPV) and store-operated calcium entry in pulmonary venous smooth muscle, providing new insight into the pathogenesis of PH (89). Furthermore, he demonstrated the role of HIF-1-BMP2/4-TRPC pathway in hypoxic PH, which held great implications for future research (90, 91). Qinghua Hu (Huazhong University of Science and Technology) and coworkers have focused on the molecular mechanisms and pathophysiological significance of calcium signal kinetics-regulated downstream cellular events in PH. His work demonstrated calcium oscillation frequency cooperates with reactive oxygen species to efficiently regulate agonist-stimulated gene expression (92) and established that calcium oscillation frequency regulates transcription and gene expression through cumulated spike duration (93). He also revealed a novel mechanism underlying hypoxic pulmonary vasoconstriction as the critical role of calcium-sensing receptor in orchestrating reactive oxygen species and Ca^{2+} signaling (94) and suggested glyceraldehydes-3-phosphate dehydrogenase plays a critical role in determining the superior functions of female BM-MSC in cell therapy against PH by regulating Ca^{2+} signal-associated cellular behaviours (95). Chen Wang and coworkers first demonstrated that the changes in membrane translocation and protein expression of cPKCα, βI, βII and nPKCδ are involved in the development of hypoxia-induced rat PH (96). He also confirmed that the septal angle is a useful tool for estimating pulmonary vascular resistance in patients with chronic thromboembolic PH (97). Notch signaling has been implicated in the development of PH, and soluble Jagged1 (sJag1) inhibits this signaling pathway. Yongguang Xiao (Wuhan

University) and coworkers demonstrated that the potential therapeutic use of the sJag1 may inhibit the proliferation of pulmonary arterial smooth muscle cells (PASMCs) and restore the differentiated PH-PASMCs phenotype by interference with Notch-Herp2 signaling (98). Jinchuan Yan (Jiangsu University) and coworkers provided evidence that docosahexaenoic acid effectively suppressed hypoxia-induced PASMCs proliferation, migration, phenotype modulation and ERK1/2 activation *in vitro* (99). Bo Zhang (Fourth Military Medical University) and coworkers demonstrated oxymatrine treatment attenuated right-ventricular systolic pressure and pulmonary arterial remodeling by suppressing expression of inflammatory cytokines and accumulation of leukocytes and T cells. Under hypoxic conditions, oxymatrine significantly upregulated expression of Nrf2 and antioxidant protein superoxide dismutase-1 (SOD1) and HO-1, but down-regulated hydroperoxide levels in PASMCs (100). Hypoxic-inducibe p27 in pulmonary artery SMCs inhibited the hypoxia-induced proliferation of pulmonary artery SMCs and arrested more cells at G0/G1 phase, and ultimately prevented hypoxic PH development (101). Liangxing Wang (Wenzhou Medical University) and coworkers reported recently salidroside, an active ingredient isolated from Rhodiola rosea, can attenuate chronic hypoxia-induced PH by promoting PASMCs apoptosis via an A2aR related mitochondria dependent pathway (102).

Pleural diseases

Huanzhong Shi and his coworkers have extensively explored the roles of $CD4^+CD25^+$ T cells, Th17 cells, Th22 cells and Th 9 cells in the pathogenesis of malignant pleural effusion (MPE) and tuberculosis pleural effusion (TPE). Upregulated $CD4^+CD25^+$ T cells express high levels of Foxp3 transcription factor, potently suppressing the proliferation of $CD4^+CD25^+$ T cells in MPE, and cytotoxic lymphocyte-associated antigen-4 is involved with the suppressive activity of pleural $CD4^+CD25^+$ T cells (103). CCL22 may be responsible for the infiltration of $CD4^+CD25$(high) T cells into the pleural space (104). The accumulation of Th17 cells in MPE predicted improved patient survival whereas increased Th22 cell numbers in MPE promoted the proliferation and migratory activity of cancer cells (105, 106). Th9 cells in both MPE and blood expressed increased CCR6 upon their surface. Furthermore, anti-CCL20 mAb significantly inhibited the ability of MPE or supernatants to stimulate Th9 cell chemotaxis. The majority of Th9 cells in MPE exhibited effector memory cell phenotype (107). Another

study performed also by Shi *et al.* showed Th17/Treg imbalance exists in MPE and pleural $CD39^+$ Tregs inhibit generation and differentiation of Th17 cells via a LAP-dependent mechanism (108). These data provide the basis for developing immune-boosting treatment strategies for MPE.

In TPE, the increased pleural $CD4^+CD25^+$ T cells express increased Foxp3 transcription factor (109). Pleural mesothelial cells (PMCs) were able to function as antigen-presenting cells to stimulate $CD4^+$ T-cell proliferation and Th22-cell differentiation. The overre-presentation of Th22 cells in TPE may be due to pleural cytokines and PMC-produced chemokines. These data suggest a collaborative interply between PMCs and Th22 cells in TPE (110). Shi's study also suggested IL-27 in pleural fluid is a sensitive and specific bio-marker for diagnosing TPE (111). Changyou Wu (Sun Yat-sen University) and coworkers demonstrated natural killer (NK) cells from TB pleural fluid cells (PFCs) expressed significantly higher levels of chemokine receptor type-3 (CXCR3) and CXCR4 than NK cells from peripheral blood mononuclear cells (PBMCs). IP-10 and SDF-1 induced more NK cell migration from PFCs than PBMCs. $CD45RO^+$ but not $CD45RO^-$NK cells produced significantly greater levels of IFN-γ, in IL-12-dependent fashion (112).

Sleep disordered breathing

Fang Han (Beijing University) and coworkers have studied narcolepsy in China. His initial retrospective study analyzed narcolepsy onset in 629 subjects diagnosed in Beijing (1998–2010), and reported the occurrence of narcolepsy onset was seasonal, peaking in April, and researching nadir in November, with a 6.7-fold increase from trough to peak. Studying year-to-year variation, he revealed a threefold increase in narcolepsy onset following the 2009 H1N1 winter influenza pandemic (113). He organized a study on gene polymorphisms in Chinese patients with narcolepsy. While there is a strong multiethnic association of polymorphisms in the TCRA and P2RY11 with narcolepsy, but his study does not confirm the association of CPT1B/CHKB in the Chinese population (114). The decreased hypoxic responsiveness in the narcolepsy-cataplexy group is a result of DQB1*0602 status rather than the clinical features of disease (115). Yuanmin Luo (Guangzhou Medical College) and coworkers reported diaphragm electromyography (EMGdi) may be a useful adjunct in measuring esophageal pressure (Pes) for the assessment of neural drive in patients with obstructive sleep apnoea (OSA). Both Pes and EMGdi measurements are useful in accurately

differentiating central from obstructive respiratory events (116). Luo *et al.* also demonstrated the dead space loading (DSL) was associated with an earlier onset of intolerable dyspnea. During exercise in the presence of an increased external dead space, DSL-induced increases in exertional dyspnea intensity ratings reflected, at least partly, awareness of increased neural respiratory drive, contractile respiratory muscle effort and ventilatory output (117). Chunshui Yu (Tianjin Medical University) and coworkers showed OSA specifically affected the cognitive and sensorimotor-related brain networks but not the visual and auditory networks. This may be a possible explanation for the impaired cognitive and motor functions in OSA (118). Using a canine model, Yue Li (Harbin Medical University) found chronic OSA could shorten atrial effective refractory period, induce altered expression of important channel proteins, and finally lead to atrial structure remodeling (119).

Lung transplantation

Since 2002, more than 200 cases of lung transplantation (LT) have been performed in the mainland of China. Jinyu Chen (Wuxi People's Hospital) and Genin Jiang (Tongji University) have done most LT cases. Chen did 100 cases, including 72 single LT and 28 bilateral LT cases. The mean survival time of these cases was 3.4 years. Jiang has performed over 60 cases of lung transplantation. The cumulative survival rate of his centre was 78%, 70%, 70% and 42% at 1, 3, 5 and 6 years, respectively, (120, 121). Lung ischemia/reperfusion injury remains a significant problem after LT. Using a rat model of LT, Chunxue Bai and coworkers determined curcumin is an alternative therapy for protecting against LT-associated injury by suppressing nuclear factor κB-mediated expression of inflammatory genes (122). Intratracheal administration of p38α shRNA plasmids provided similar therapeutic effects (123). Jingxiang Wu (Shanghai Jiaotong University) and coworkers demonstrated cystathionine-g-lyase protein expression and H_2S generation were dramatically decreased in transplanted rat lungs. NaHS administration significantly improved pulmonary function, decreased lipid peroxidation, lowered myeloperoxidase activity, inhibited IL-1β production and increased IL-10 levels in graft lung tissues. This study suggested H_2S modulation may be a potential therapeutic approach to LT (124).

Prospect

With the development of China's economy in recent years, the NSFC increases the support in the field of respiratory science. Scholarly exchanges and collaborations from China's premiere experts with international peers continue to grow. Currently, increasing numbers of Chinese scientists in the United States and Europe have relocated to China, become leaders in the respiratory field, and devote their abilities and expertise to the advancement of respiratory medicine.

Within the next 5–10 years, the NSFC will continue to stimulate the basic research of diverse respiratory diseases, including chronic airway diseases, ALI, lung infection, pulmonary hypertension, IPF and sleep disorder. With fast economic development and environment deterioration, the NSFC particularly prompts active research work on environmental factors-related respiratory diseases. In recent years, NSFC has been encouraging the translation of basic discoveries into clinical practice, and also the communication of research advances to the public.

The NSFC processes the applications it receives by means of robust peer review, the best form of review internationally. Its research-funding mechanisms have proven to be a successful example of reform of China's traditional science and technology system, thereby improving the entire Chinese research culture (125). We believe that the NSFC will continue to actively support the development and advancement of respiratory medicine in China.

Acknowledgements

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