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A comprehensive retrospect on the current perspectives and future prospects of pneumoconiosis

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Pneumoconiosis is a widespread occupational pulmonary disease caused by inhalation and retention of dust particles in the lungs, is characterized by chronic pulmonary inflammation and progressive fibrosis, potentially leading to respiratory and/or heart failure. Workers exposed to dust, such as coal miners, foundry workers, and construction workers, are at risk of pneumoconiosis. This review synthesizes the international and national classifications, epidemiological characteristics, strategies for prevention, clinical manifestations, diagnosis, pathogenesis, and treatment of pneumoconiosis. Current research on the pathogenesis of pneumoconiosis focuses on the influence of autophagy, apoptosis, and pyroptosis on the progression of the disease. In addition, factors such as lipopolysaccharide and nicotine have been found to play crucial roles in the development of pneumoconiosis. This review provides a comprehensive summary of the most fundamental achievements in the treatment of pneumoconiosis with the purpose of indicating the future direction of its treatment and control. New technologies of integrative omics, artificial intelligence, systemic administration of mesenchymal stromal cells have proved useful in solving the conundrum of pneumoconiosis. These directional studies will provide novel therapeutic targets for the treatment of pneumoconiosis.

KEYWORDS

pneumoconiosis, inflammation, fibrosis, current status, cell therapy, nanotechnology

1 Introduction

Pneumoconiosis is an incurable but preventable interstitial lung disease caused by occupational inhalation and retention of dust particles (1), such as silica dust, coal mine dust, and asbestos fibers (2). The definition of pneumoconiosis varies from country to country. National Institute for Occupational Safety and Health of USA defines

pneumoconiosis as a group of lung diseases caused by the lung's reaction to inhalation of certain dusts (3), and the main cause of the pneumoconiosis is work-place exposure and environmental exposures have rarely been related to these diseases (4). This definition underscores the connection between pulmonary reaction and work place. Pneumoconiosis in the UK is defined as a pulmonary disease caused by inhalation of dust and its retention in the lungs. In China, pneumoconiosis is defined as a disease mainly characterized by diffuse fibrosis of lung tissue caused by long term inhalation of productive mineral dust and their retention in the lungs during occupational activities. Unlike two definitions in the USA and UK, this definition in China focuses on the mineral dust and pulmonary fibrosis.

The emergence of new materials and new industries, such as denim jean production, domestic benchtop fabrication, and jewelry polishing, has resulted in a rising trend of pneumoconiosis, underscoring the need to be cautious about identifying and controlling the sources of novel occupational exposure (5). Although pneumoconiosis is preventable, its incubation period is long and clinical symptoms are not obvious in the early stage. In addition, it could be very difficult to distinguish pneumoconiosis from other lung diseases, including lung cancer, tuberculosis, and sarcoidosis, due to its prolonged latency and similar clinical symptoms (6). Because no effective treatment methods have been established (2), early diagnosis and timely intervention are vital to patients with pneumoconiosis. Therefore, it is of much significance to develop and apply novel diagnostic biomarkers, methods, and therapeutic targets.

This review article aims to provide a more in-depth analysis of the specific pathogenesis, novel diagnostic biomarkers and technologies, new therapeutic targets, prospective drugs, and promising treatments of pneumoconiosis that may be applied on a large scale in the future.

The paper begins with the international and national classifications and epidemiological characteristics of pneumoconioses. Then we broaden the understanding on the strategies for prevention, clinical manifestations, and diagnosis. In the diagnosis of pneumoconiosis, we respectively describe current status of pneumoconiosis diagnosis, prospective biomarkers for diagnosis, and advanced diagnostic techniques. Moreover, to uncover this disease's pathogenesis, autophagy, apoptosis, pyroptosis, and epigenetics on the progression of pneumoconiosis are expressly analyzed. Finally, therapeutic approaches to pneumoconiosis are presented for future investigations, which include the promising targets, promising drugs and other therapies for pneumoconiosis.

2 Methodology

Articles were therefore reviewed by searching PubMed, Scopus, Web of Science, Web of Knowledge, Medline, and Google Scholar. The following key words were retrieved: “pneumoconiosis,”

“evolution,” “classification,” “prevention,” “manifestation,” “diagnosis,” “pathogenesis,” “inflammation,” “fibrosis,” “therapy,” “treatment,” etc.

3 International and national classifications of pneumoconioses

Specific kinds of pneumoconioses are listed as occupational diseases by International Labor Organization (ILO) and Chinese government. Based on *The Occupational Diseases Catalogue, 2010 edition* released by ILO, pneumoconioses can be divided into two types: pneumoconiosis caused by fibrous mineral dust and pneumoconiosis caused by non-fibrous mineral dust (7). In the *Classification and Catalogue of Occupational Diseases, 2013 Edition* released in China, twelve kinds of pneumoconioses have been listed as statutory occupational diseases, including silicosis, coal workers' pneumoconiosis, graphite pneumoconiosis, carbon black pneumoconiosis, asbestosis, talc pneumoconiosis, cement pneumoconiosis, mica pneumoconiosis, kaolin pneumoconiosis, aluminosis, electric welder pneumoconiosis, and foundry worker pneumoconiosis. Since it is sometimes difficult to determine the main cause of pneumoconiosis, people still name the disease according to the patients' occupations, such as welder's pneumoconiosis and grinder's pneumoconiosis.

Apart from above kinds of pneumoconioses listed as occupational diseases, several classification systems of pneumoconioses have been devised over the years on different criteria. The specific classifications of pneumoconioses in some countries and regions are listed in [Table 1](#). According to *International Classification of Diseases, 11th Edition*, pneumoconioses can be divided into 11 major categories, and there are three subgroups of pneumoconiosis caused by siliceous dust. In Japan, silicosis in miners was not identified as an occupational disease until 1930. Silicosis caused by free silica dust and silicosis with tuberculosis were identified as occupational diseases in 1936 (8). Several other types of pneumoconiosis, such as asbestosis and talc pneumoconiosis, were also added. Based on the recommendation of National Institutes of Health of USA, pneumoconioses can be divided into five types: silicosis, asbestosis, coal workers pneumoconiosis, other kinds of pneumoconiosis, and benign pneumoconiosis (9). European Union classified pneumoconioses into four categories: silicosis, silicosis with tuberculosis, asbestosis, and pneumoconiosis caused by silicate dust. Only three types of pneumoconiosis are identified in India, including silicosis, asbestosis, and coal workers pneumoconiosis (10). In China, pneumoconioses can be divided into five categories based on the type of dust inhaled: silicosis caused by inhalation of dust containing free silica; silicate lung caused by inhalation of dust containing silica such as asbestos, mica, and nephelite; carbon pneumoconiosis caused by inhalation of coal, graphite, activated carbon, carbon black and other powders; mixed pneumoconiosis caused by inhalation of dust containing free silica and other types of dust (organic dust, inorganic dust, synthetic dust); and other pneumoconioses, caused by metal or other compounds, such as aluminum, and glass wool (11).

TABLE 1 International and national classifications of pneumoconioses.

Nation	Number of categories	Type
International level	11	Pneumoconiosis caused by silica dust (CA60.0) Talc pneumoconiosis (CA60.00) Specific pneumoconiosis caused by silica dust (CA60.0Y) Unspecified pneumoconiosis caused by silica dust (CA60.0Z) Coal workers' pneumoconiosis (CA60.1) Pneumoconiosis caused by mineral fibers (CA60.2) Pneumoconiosis related to tuberculosis (CA60.3) Aluminosis (CA60.4) Pulmonary bauxite fibrosis (CA60.5) Berylliosis (CA60.6) Pulmonary graphite fibrosis (CA60.7) Siderosis (CA60.8) Tin pneumoconiosis (CA60.9) Other specific pneumoconioses (CA60.Y)
Japan	8	Silicosis Asbestosis Welder's lung Coal workers pneumoconiosis Aluminum pneumoconiosis Indium pneumoconiosis Beryllium pneumoconiosis Cemented carbide pneumoconiosis
America	5	Silicosis Asbestosis Coal workers' pneumoconiosis Other kinds of pneumoconioses Benign pneumoconiosis
European Union	4	Silicosis Silicosis with tuberculosis Asbestosis Pneumoconiosis caused by silicate dust
China	5	Silicosis caused by inhaling dust containing free silica Silicosis caused by inhaling dust containing silica Carbon pneumoconiosis Mixed pneumoconiosis Other pneumoconioses
India	3	Silicosis Asbestosis Coal workers' pneumoconiosis

4 Epidemiological characteristics of pneumoconiosis

According to the *Global Burden of Disease Study 2019*, a total of 0.20 (0.17–0.23) million new cases of pneumoconiosis were diagnosed and 0.92 (0.76–1.12) million disability-adjusted life years (DALYs) were calculated in the year 2019, implying that pneumoconiosis is still a major concern worldwide (12). Based on the *Global Burden of Disease Study 2017*, cases of pneumoconiosis have increased in the five sociodemographic index regions from 1990 to 2017 while the age-standardized incidence rates (ASIR) have shown a downward trend. A reduction

was observed in ASIR of silicosis, coal workers' pneumoconiosis (CWP), and other pneumoconioses. However, the ASIR of asbestosis displayed an increasing trend (13). Increase in ASIR of asbestosis was the biggest in high-income continents like North America and Australasia, suggesting the importance of intensifying the controlment of asbestos in the market. In addition, higher incidence of pneumoconiosis was observed in males than in females. Besides, the highest ASIRs in 2017 were noted in China, Papua New Guinea, and North Korea. Middle- Socio-demographic Index regions had the highest ASIR of pneumoconiosis. The ASIR of pneumoconiosis is inversely correlated with human development index (14).

Distinct occurrence patterns of pneumoconiosis have been reported in different countries and regions (13). For example, in America, pneumoconiosis-associated-deaths decreased by 40.4% from 1999 to 2018. CWP (69.6%) and silicosis (53.0%) accounted for the largest proportion of declining cases. On the other hand, asbestosis was the most reported pneumoconiosis, which was consistent with the world epidemic trends of pneumoconiosis. The matter of concern was that the incidence of pneumoconiosis due to other inorganic productive dust increased dramatically (e.g., aluminum, bauxite, beryllium, iron, and tin oxide) (1). Notably, the national prevalence of CWP among working coal miners is increasing, especially in central Appalachia, which will likely be reflected in future trends for severe and disabling disease, including progressive massive fibrosis (15), and it is speculated that the nano-sized coal dust is likely to be one of the reasons for the increase in the prevalence of CWP (16).

China suffered from the world's largest health loss from pneumoconioses in 2019, accounting for two-thirds of the global health loss from pneumoconiosis (2). According to the *Occupational Diseases Report in 2021*, 11,809 newly reported cases of occupational pneumoconiosis were diagnosed in China, accounting for 77.65% of all new occupational disease cases, making it urgent to prevent and control pneumoconiosis. Newly diagnosed cases and DALYs of pneumoconiosis continued to rise during 1990–2019 in China. However, age standardized calculation showed a significant downward trend in the incidence, death, and DALY rates due to pneumoconiosis, with the exception of incidence of silicosis and asbestosis-associated mortality (2). This achievement was mainly attributed to the unremitting efforts of Chinese government. Other factors which contributed to this decline include intensified regulatory supervision, expanded in medical accessibility, and improved medical treatment. In China, silicosis accounted for the largest proportion of confirmed pneumoconiosis cases, followed by CWP, other pneumoconiosis, and asbestosis in 2019 (17). Notably, the age-standardized death rate of pneumoconiosis in western China was higher than that in the eastern coastal area of China, and there is an urgent need for adequate supervision and medical services of occupational diseases in Western China (2). Additionally, new cases, deaths, and DALYs due to pneumoconiosis in males accounted for approximately 95% of the corresponding total numbers in 2019, which was consistent with previous reports (2).

Accurate data on the prevalence of pneumoconiosis is essential for health resource planning and policy development. In 2016,

pneumoconiosis was found to have caused 21,488 deaths worldwide (13). However, it must be pointed out that the actual burden of pneumoconiosis in China may be greater than reported, which could be caused by the following factors. First, due to the low frequency of occupational health examinations and absence of strict diagnostic criteria for pneumoconiosis (18), timely diagnosis is not available for all potential patients in relevant industries, leading to an underestimate of existing cases. Secondly, workers in small industrial enterprises or small informal workshops tend to solve health and safety problems by themselves, and such cases go unreported (19). Thirdly, the frequent flow of migrant workers and long incubation period of pneumoconiosis can also result in underreporting (2). Besides, some workers are reluctant to take a physical examination, especially a chest examination for fear of losing jobs, even if relevant symptoms have appeared (20).

With the emergence of new industries, such as denim jean production, benchtop fabrication, and jewelry polishing (5), the incidence of pneumoconiosis, especially silicosis, is increasing. Workers may inhale fumes containing sand and other toxic chemicals while sandblasting, which is used to get the look of buff pants (21). The incidence of silicosis is on the rise in Spain, Australia, and some other regions where artificial stones (AS) get popular (6). Unlike natural stone associated silicosis, AS-associated silicosis was characterized by short latency, rapid radiological progression, accelerated decline in lung function, and high mortality (17). The respirable crystalline silica (RCS) is a by-product of AS production, and the dust is composed of inhalable particles with a diameter usually smaller than 5 μm (6). RCS could be disregarded easily because it is colorless, odorless, and accumulates quickly. Much exposure to RCS has been reported to result in the occurrence and progression of silicosis (6). Likewise, increase in the use of nanomaterials due to the emergence of nanotechnology, in which the generated nanoparticles are cytotoxic to lung epithelial cells, has resulted in a higher incidence of pulmonary inflammation and fibrosis (22).

5 Strategies for preventing pneumoconiosis

Although pneumoconiosis poses a major threat to global public health, preventive measures can be taken to reduce its harm. Medical workers need to perform follow-up visits for key populations, including patients diagnosed with advanced pneumoconiosis at first diagnosis, patients of older age, and patients with prolonged exposure to dust, and strict supervision should be carried out in industries with high incidence of pneumoconiosis, such as coal mining and construction (23).

Workers at risk of pneumoconiosis need occupational safety education to raise their awareness of personal protection, ensuring that they are responsible for their health (1). Rapid progression of pneumoconiosis in miners has been reported to be strongly correlated with exposure to high concentrations of mineral dusts (24), indicating the necessity of clean working environment.

Employers and business enterprises should ensure that sufficient personal protective equipment forms an indispensable part of the workers' gear. Workers can use filter type dustproof respiratory protective equipment to prevent the inhalation of dust in the working environment. Protective efficiency of filtering dust respirators relies on the properties of filter materials, from which filters are made, and the structure of a half mask frame. A new half mask frame design has been proposed, which is flexible and fits the face surface well (25). The priority is to improve the controlling measures, including elimination, substitution, and exhaust ventilation, in addition to the supply of respirators (6). It is important to use technical measures of ventilation, dust removal, detoxification, noise reduction, and isolation, to eliminate dust hazards. Wet dedusting is the main coal dust suppression technique commonly used in coal mines, and coal wettability is the main factor that influences dust suppression efficiency (26). Based on the two-fluid (Euler-Euler) frame model, a mathematical model for wet dedusting process has been established to explore the effect of particle size distribution of the dust particle, spray flow, and ventilation rate on the dedusting efficiency of wet dedusting method. This model revealed that droplets with a diameter between 15 μm and 70 μm can ensure high capture efficiency of respirable dust, and that spray quantity and dedusting efficiency are not necessarily proportional (27). Another mathematical model was proposed for cyclonic spray dedusting, and the spray can be used to promote agglomeration of particles and improve the dust removal efficiency in the swirl field (28). With the increased attention toward pneumoconiosis and rapid development of science and technology, several novel wet dedusting technologies have been invented, including pneumatic spiral spray system (29), novel wind-assisted centralized spraying dedusting device (30), and pre-injection foam dedusting technology (31). With remarkable dust suppression performance, these technologies can help to improve the work environment effectively. Furthermore, employers should provide some medical services for workers in the forms of health questionnaires, physical examination, lung function, and chest radiology (6). Moreover, both employers and health care providers should inform relevant public health agencies of the identification of cases, so that timely interventions can be performed and adequate treatment can be administered to patients with pneumoconiosis (23, 32).

Government should improve surveillance and guarantee systems of occupational diseases, step up the intensity of regulatory surveillance, and instruct employers to standardize the protocols of safe production (1). It is also necessary to increase the investment in frontier research and technology development to explore novel measures of prevention. Meanwhile, the government should encourage the use of replaceable and harmless productive materials to reduce the incidence of pneumoconiosis (2). A systematic review indicates that exposed workers suffer from a higher risk of lung cancer when asbestosis or silicosis is present (33). Attention should also be paid to pneumoconioses caused by other inorganic dust, for the incidence rate is rising in recent years. Inhalation of silica dust is correlated with systemic autoimmune diseases (34), and it is important to take an occupational history in patients with autoimmune diseases to improve recognition of workplace silica exposure (32).

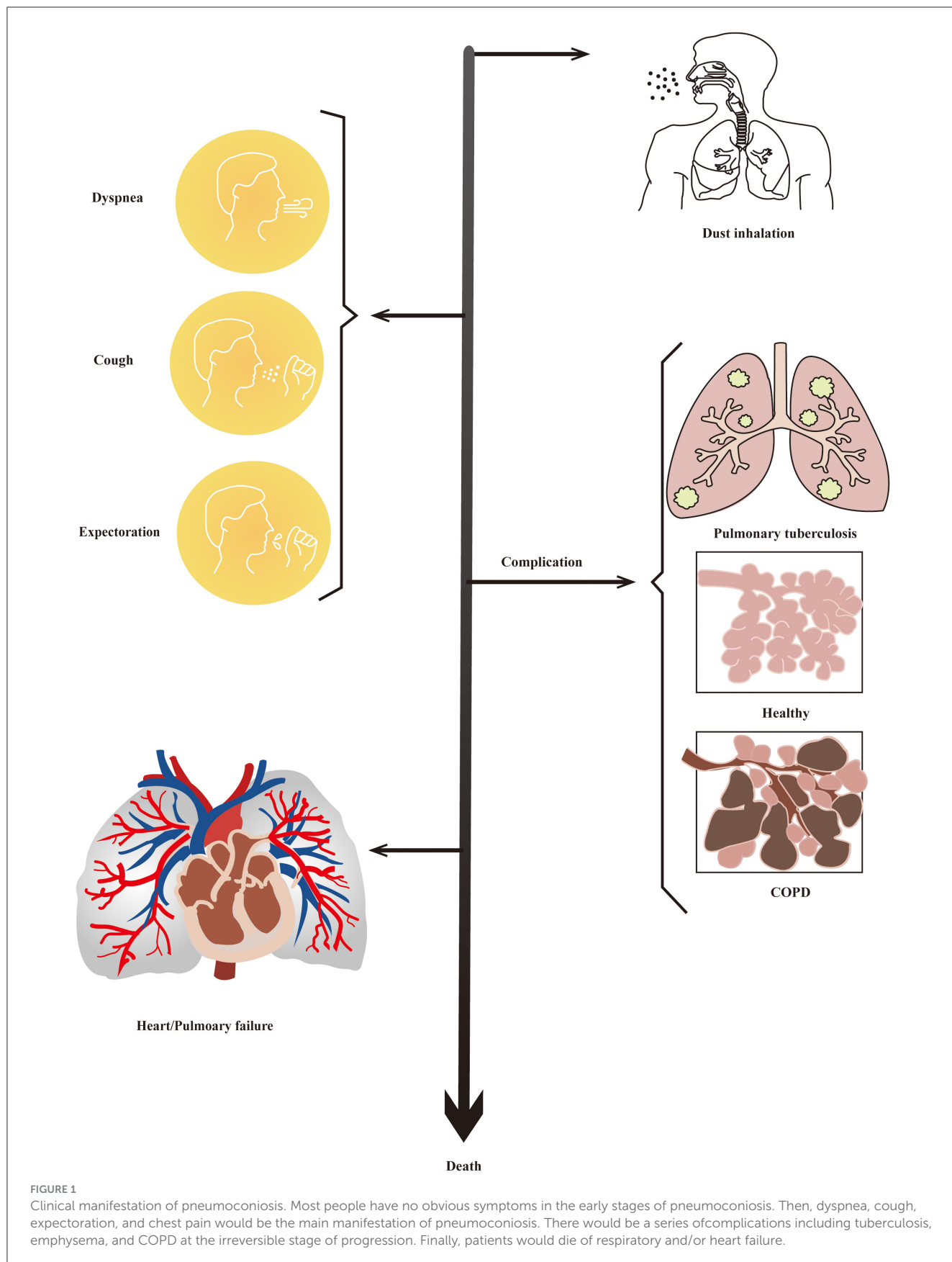


FIGURE 1
 Clinical manifestation of pneumoconiosis. Most people have no obvious symptoms in the early stages of pneumoconiosis. Then, dyspnea, cough, expectoration, and chest pain would be the main manifestation of pneumoconiosis. There would be a series of complications including tuberculosis, emphysema, and COPD at the irreversible stage of progression. Finally, patients would die of respiratory and/or heart failure.

6 Clinical manifestations and diagnosis of pneumoconiosis

6.1 Clinical manifestations

The incubation period of pneumoconiosis is long, and the majority of the patients do not show any obvious symptoms. The main clinical manifestations of pneumoconiosis are dyspnea, cough, expectoration, and chest pain (23), which appear after persistent exposure to mineral dusts. Most of patients are often in the irreversible stage with a series of complications, including tuberculosis, emphysema, and chronic obstructive pulmonary disease (COPD) (2, 35). Pulmonary inflammation and progressive fibrosis are typical pathological changes of pneumoconiosis, which can result in respiratory and/or heart failure (36). Clinical manifestation and the developing process of pneumoconiosis is shown in Figure 1.

6.2 Diagnosis of pneumoconiosis

6.2.1 Current status of pneumoconiosis diagnosis

Pneumoconiosis is diagnosed on the basis of functional changes of lungs identified by pulmonary function test (PFT) and morphological changes of lungs determined by radiological findings, including computed tomography (CT) scanning of the chest, chest radiography, or lung biopsy findings in conjunction with occupational history exposure to mineral dust, clinical manifestations, and working environment (23, 32, 37, 38). PFT shows that patients have normal ventilation function in early stage of pneumoconiosis, and their dispersion function decreases during middle and late stages with varying degrees of restrictive or obstructive ventilation disorders. Besides, auxiliary examinations also include X-rays and arterial blood gas analysis. Arterial blood gas analysis shows patients of pneumoconiosis suffer from hypoxemia, and hypercapnia aggravates the situation in advanced stage. As common characteristics of pneumoconiosis, Pulmonary inflammation, and fibrosis can be used as diagnostic clues (6).

It indicates the possibility of pneumoconiosis if there are presence of nodular or reticulonodular lesions in chest radiography or small nodules with peri lymphatic distribution on thin-section CT with or without eggshell calcifications in the population exposed to dust (39). Current diagnostic criteria are based on the *International Labour Organization/International Classification of Radiograph of Pneumoconiosis (ILO/ICRP), 2011 Edition*, which contains a set of digital standard images. The X-ray images of pneumoconiosis are characterized by small opacities and pleural plaques, which are not specific to this disease (23). ILO has subdivided pneumoconiosis from three aspects: technical quality, substantial abnormalities, and pleural abnormalities. According to the guidelines of ILO/ICRP, parenchymal abnormalities of pneumoconiosis can be divided into small opacities and large opacities. Small opacities have three subdivisions in profusion, shape and size, and mixed. Large opacities have four levels of 0, A, B, and C. Based on the *GBZ70-2002-Diagnostic Criteria for Pneumoconiosis*, China divides the progression of pneumoconiosis into three stages, and the radiographic criteria include the overall density of small opacities, lung range of small opacities,

TABLE 2 The diagnostic stages of pneumoconiosis in China.

Diagnostic stages	Reference symptoms
Stage I	<ul style="list-style-type: none"> a) There is a small opacity with an overall density of 1, which is distributed in at least 2 lung regions. b) Exposure to asbestos dust showed a small opacity with an overall density of 1, distributed in only 1 lung area, and pleural plaques appeared. c) Exposure to asbestos dust resulted in an overall concentration of small opacities of 0, but a concentration of small opacities of 0/1 in at least two lung areas accompanied by pleural plaques (People with one of these symptoms can be diagnosed with pneumoconiosis.)
Stage II	<ul style="list-style-type: none"> a) There is a small opacity with an overall density of level 2, distributed over 4 lung regions. b) There was a small opacity with an overall density of level 3, and the distribution range reached 4 lung regions. c) Exposure to asbestos dust, a small opacity with an overall density of 1, distributed in more than 4 lung areas, with pleural plaques that have involved part of the heart margin or diaphragmatic surface. d) Exposure to asbestos dust, with a small opacity of overall concentration level 2, distributed over 4 lung areas. Pleural plaques are present at the same time and have involved part of the heart margin or diaphragmatic surface. (People with one of these symptoms can be diagnosed with pneumoconiosis.)
Stage III	<ul style="list-style-type: none"> a) There is a large opacity with a long diameter of no <20 mm and a short diameter of no <10 mm. b) There are small opacities with an overall density of level 3 distributed over 4 lung regions with small shadow clusters. c) There is a small opacity of total intensity level 3 and the distribution range is more than 4 lung regions with large shadow. d) Exposure to asbestos dust presents a small opacity with an overall concentration of grade 3, covering more than 4 lung regions, and the length of a single or multiple pleural spots on both sides exceeds half of the length of the unilateral chest wall or involves the heart margin and makes it partially disheveled. (People with one of these symptoms can be diagnosed with pneumoconiosis.)

and whether small opacities converge into big opacities, pleural plaques or other symptoms, China divides pneumoconiosis into three stages based on the GBZ70-2002-diagnostic criteria for pneumoconiosis. Specific diagnostic criteria for each stage are listed in Table 2.

Notably, it is not easy to distinguish pneumoconiosis from lung cancer, tuberculosis and sarcoidosis due to prolonged latency and similar clinical symptoms (6). With the rapid development of technologies, magnetic resonance imaging has proven useful in distinguishing progressive massive fibrosis from lung cancer (39). Bronchoalveolar lavage fluid can also be used to detect the biomarkers of pneumoconiosis, which will be of much helping accurate diagnosis.

6.2.2 Prospective biomarkers in pneumoconiosis diagnosis

Early and accurate diagnosis of pneumoconiosis is difficult due to the delayed appearance of clinical manifestations and the complexity of the diagnostic procedures, and this is why the

TABLE 3 The biomarker of pneumoconiosis.

Biomarker	Expression level	Tissue/cell/patients	References
HO-1	Up	Blood serum	(40)
PGD	Up	Human lung tissue	(41)
Thromboxane A (TXA)	Up	Human lung tissue	(41)
IL-8	Up	Blood serum	(42)
Tumor necrosis factor α (TNF- α)	Up	Blood serum	(42)
HECTD1	Up	AMs and RAW264.7 macrophage cell line	(44)
High-mobility group box-1 (HMGB-1)	Up	Blood serum	(53)
Apoptosis of AMs	Up	Patients with silicosis	(46)
circulating double-stranded DNA	Up	Sputum	(54)
C-X-C motif chemokine ligand 10	Up	Sputum	(54)
Krebs von den Lungen 6	Up	Blood serum	(55)
Surfactant protein-D	Up	Blood serum	(55)
Matrix metalloproteinase-2	Up	Blood serum	(55)
Npnt	Up	Patients with silicosis	(45)
Activating transcription factor 3	Up	Patients with silicosis	(43)
Propylparaben	Up	Blood serum	(56)
Has-miR-4516	Up	Blood serum	(48)
Circular RNA hsa_circ_0058493	Up	Peripheral blood	(57)

majority of the patients are already in the advanced stage at the time of diagnosis, when the condition is irreversible and no effective treatment is available. Fortunately, with the deepening research on the pathogenesis of pneumoconiosis in the recent years, new biomarkers have been discovered and can be potentially used as novel diagnostic tools. Prospective biomarkers of pneumoconiosis in the process of diagnosis are summarized in Table 3.

A previous study on patients with silicosis and BALB/c mice shows that increasing the content of pulmonary heme oxygenase-1 (HO-1) can inhibit the activity of reactive oxygen species (ROS) and subsequent pathologic changes, thereby attenuating progression of silicosis (40). Cytokines and inflammatory factors, as well as proteins, can be helpful in the diagnosis and treatment of pneumoconiosis. Some cytokines and inflammatory factors, such as interleukin (IL-8) and Prostaglandin D (PGD), can be used as indicators of pneumoconiosis (41, 42). Transcription factor 3, an inflammatory repressor, can be activated for early diagnosis of silicosis (43). In addition, changes in the expression of some proteins can also be used for the diagnosis of pneumoconiosis. For example, HECT domain E3 ubiquitin ligase 1 (HECTD1) may serve as a potential marker of silicosis, as it promotes silica-induced activation of macrophages via ubiquitination, thereby inducing proliferation and migration of fibroblasts (44). Similarly, development of fibrosis can be recognized by serum nephronectin (Npnt), which is a new member of the integrin family of ligands, suggesting that Npnt seems to play a role in the progression of fibrosis with other cytokines and can be used in the diagnosis of pneumoconiosis (45). Alveolar macrophages (AMs) apoptosis could be used as a potential biomarker for human silicosis,

which promotes the development and progression of silicosis via activating the fatty acid synthetase (Fas)/fatty acid synthetase ligand (FasL) pathway (46).

MicroRNAs (miRNA) have great application prospects as biomarkers in diagnosing pneumoconiosis, and they may serve as indicators of organ or cell-specific toxicity, disease, and biological status (47). It is noteworthy that has-miR-4516 targeted genes encodes basonuclin2, inhibitors of growth family member 4, the potassium voltage-gated channel, and “sha-1-related subfamily member 1” proteins, which shows that has-miR-4516 could be used as a potential biomarker of pulmonary fibrosis progression in patients with pneumoconiosis (48). Besides, an increase was observed in miR-107 in serum exosomes and lung tissue in the experimental silicosis mouse model, while the inhibition of miR-107 reduced pulmonary fibrosis, which provided a rationale for using miR-107 for intervening in silicosis progression (49). However, miRNAs have not been routinely used as non-invasive biomarkers, for lack of standard approaches to sample preparation and miRNA measurement, as well as uncertainty in their biological interpretation (50).

Circular RNAs (circRNAs) are non-coding RNAs with a closed loop structure, and they are identified as competing endogenous RNAs (ceRNAs) serving as a sponge for miRNA through complementary base pairing (44). Long non-coding RNAs (lncRNAs) are a large class of non-coding transcripts of >200 in length with no protein-coding capacity, and they are involved in chromosome modification, transcription and post-transcriptional processing (51). Several studies have demonstrated that lncRNAs can function as ceRNAs in the

process of fibrosis by binding to and undergoing crosstalk with miRNAs, and more relevant research can be conducted on lncRNAs (52).

6.2.3 Advanced diagnostic techniques for pneumoconiosis

With the rapid development of science and technology, more and more diagnostic methods have been developed for the diagnosis and assessment of severity of silicosis, and high-resolution computed tomography (HRCT) and chest radiography (CR) are two of them. A previous study shows that HRCT is more reproducible and more accurate than CR in the diagnosis of early pneumoconiosis, suggesting that HRCT is more correlated with lung function test. However, the results of the study did not support the hypothesis that HRCT was more sensitive than CR in the early detection of silicosis (58). Electrical impedance tomography (EIT) can be used to detect the spatial distribution of electrical properties of tissues by measuring the transfer impedances between electrodes on the body surface (59). This technique is usually applied to functional chest examinations with the purpose of identifying patients with chronic pulmonary diseases at early stage (60). The feasibility of EIT perfusion imaging has been proved (61). Although EIT has widespread applications, uniform diagnostic criteria have not been developed, and recommendations are needed on how EIT findings can be used to generate diagnoses. Magneto pneumography was invented to investigate the remanent magnetism of foreign intrathoracic ferromagnetic particles after magnetization by an external magnetic field, and one advantage of this technique is noninvasiveness (62). A lot of work has to be done in this field before it can be widely used in clinic practice, due to its uncertainty in safety, sensitivity, and specificity (37).

Artificial Intelligence (AI) has several development prospects in the diagnosis and management of pulmonary diseases (63), such as lung nodule evaluation, tuberculosis or pneumonia detection, and quantification of diffuse lung diseases (64). Computer-aided detection based on machine learning is an emerging research field, especially artificial neural network and convolutional neural networks (64, 65), which have demonstrated significant performance gain over the classic machine learning techniques. AI-assisted radiography screening and diagnosis in occupational lung diseases has proven feasible and effective (66). CR is a near perfect domain for the development of deep learning algorithms for automatic interpretation, requiring large annotated datasets, in view of the high number of procedures and increasing data availability (64). Compared with classic machine learning techniques, deep learning methods have led to substantial performance gain (64). Zhang et al. set out to establish an AI-based model, which could help doctors to diagnose pneumoconiosis and stage the course of the disease through CR. The system of chest X-ray was created with the help of a training queue and confirmed with the help of an independent evaluation queue. Their groundbreaking study evaluated the possibility and effectiveness of AI-assisted radiological diagnosis and screening in the field of occupational lung disease (66). Zhang et al. proposed a technique of diagnosing pneumoconiosis using wrist pulse signals, in which wrist pulse signals were collected from both non-pneumoconiosis and pneumoconiosis patients, and then a single piece of pulse signal was separated. They used machine learning methods to process

and analyze the pulses, and reported that their 13-dimensional feature could be used as the main feature for the diagnosis of pneumoconiosis (67).

7 Pathogenesis of pneumoconiosis

The pathogenesis of pneumoconiosis involves several complex mechanisms. In this review article, silicosis, the most common type of pneumoconiosis, has been taken as an example to elucidate the pathogenesis of pneumoconiosis.

7.1 Basic mechanism of silicosis

Silica particles entering the distal airways and alveoli have to be RCS, with a diameter usually smaller than 5 μm (6). When these particles arrive at their destination, the alveolar macrophages (AMs) identify and swallow silica dusts through macrophage receptor with collagenous structure (MARCO) (68, 69). Silica (Si-) and Silicon monoxide (SiO-) radicals react with water to generate ROS, reactive nitrogen species, and nitric oxide (NO), which could lead to lipid peroxidation of cell membranes and apoptosis in macrophages and other cells (70). Macrophage polarization is closely associated with the occurrence and development of silicosis, and could be the key to further elucidating the pathogenesis of silicosis (71). Classically activated macrophage is the primary type of alveolar macrophage polarization occurring in the early stage of silicosis. As the disease progresses, alternatively activated macrophage gradually becomes the dominant type of polarization to promote tissue repair. Additionally, signal transducer and activator of transcription (STAT) and interferon regulatory factor signaling pathways are also involved in the process of macrophage polarization in silicosis (71). Moreover, the activation of nucleotide-binding oligomerization domain-receptor interacting protein 2-nuclear factor- κ -gene binding signaling pathway may also lead to the polarization of macrophages (72). Besides, the cyclic GMP-AMP synthase (cGAS) activates the stimulator of interferon genes (STING) and then brings about an increase in ROS generation. The cGAS-STING pathway, as a result, is crucial for silica-induced pulmonary inflammation (73). When silica particles are phagocytosed, the H-bonding reaction occurs and damages the lysosomes in AMs. Lysed lysosomes activate the inflammasome, a polyprotein complex in the cytoplasm, and the activation leads to the increased expression of inflammatory cytokines, including TNF- α , transforming growth factor β (TGF- β), and interleukin 1 β (IL-1 β). A previous study demonstrated a potential role of IL-1 β -dependent NO-mediated apoptosis in evolution of murine silicosis, thereby showing an association between apoptosis and inflammation (74).

Periodic acid-Schiff-positive material accumulation occurs in the alveoli due to dysfunction of AMs, and this accumulation is the typical characteristic of pulmonary alveolar proteinosis (PAP) (75). PAP could promote profibrotic response by transforming fibroblasts into myofibroblasts through LOC103691771 induced by TGF- β 1 (52), and PAP also would result in collagen deposition and fibrosis of lungs (76). Fibrocytes and myofibroblasts derived from lung type II epithelial cells play a crucial role in the early stage of silicosis, while myofibroblasts derived from resident lung

fibroblasts play a key role during the formative period of fibrosis (77). Additionally, the extracellular matrix-related molecules, such as integrins and their ligands including fibronectin, vitronectin, laminin, and collagens, also exert an important influence on the process of fibrosis (45). Activation of fibroblast is initiated by cluster of differentiation 44-ras homolog gene family-yes-associated protein (CD44-RhoA-YAP) signaling (78). A study demonstrated the fibrogenic effect of glycolysis through the circular RNA HIPK3 (Homeodomain-interacting protein kinase)/micro-30a-3p/Forkhead box K2 regulatory pathway, indicating the important role of glycolysis in the development of pneumoconiosis (79). Exosomal protein and miRNAs including sulphation of secreted phosphoprotein I and a miR-125a-5p derived from macrophage exosomes, used for intercellular communication, have been reported to play a key role in fibroblast trans differentiation and the development of silicosis (80, 81). Silica-exposed macrophage-derived exosomes promote the progression of fibrosis, which is mediated by endoplasmic reticulum (ER) stress (82). The basic mechanism of silicosis is presented in Figure 2.

7.2 Autophagy on the progression of pneumoconiosis

It was reported that phosphatidylinositol3-kinase/Protein Kinase B/Mechanistic Target of Rapamycin (PI3K/Akt/mTOR) signaling pathway was involved in the autophagy induced by silicon dioxide exposed, and autophagy may play a protective role in the process of pulmonary fibrosis (83). Autophagy can also be activated by the adenosine monophosphate activated protein kinase/mammalian target of rapamycin (AMPK-mTOR) signaling pathway (84). Genetic loss of Gas6 reduces the expression of Mer receptor, leading to the decline of accumulation of silica-induced autophagosomes (85). Autophagy plays a two-sided role in the occurrence of silicosis. Under normal circumstances, autophagy degrades intracellular matter to produce new building blocks and energy for cellular renovation and homeostasis (86). With the ability of reducing apoptosis of alveolar epithelial cells, autophagy could relieve silica-induced fibrosis (87). However, inhaling silica particles cause lysosomal rupture leading to excessive accumulation of autophagosomes in AMs, which may lead to apoptosis in AMs (88). ZC3H4, a member of the Cys-Cys-Cys-His (CCCH) zinc finger protein family, is involved in silica-induced endothelial-mesenchymal transition (EndoMT) through ER stress and autophagy (89). ZC3H4 was reported to regulate the secretory function of monocytes, which, in turn, inhibited fibroblast function in early inflammation through autophagy signaling, thereby reducing pulmonary fibrosis (90). ETS-like transcription factor (ELK-1) could promote epithelial mesenchymal transition (EMT) via the upstream activity of OS and downstream signaling of ZC3H4 expression (85). It was reported that silica dust exposure could induce autophagy by changing the connectivity of Beclin1 from Bcl-2 to PIK3C3 (91). Autophagy could be inhibited by FAS-caspase-8 due to the activation of TNF- α -TNF-receptor (TNF- α -TNFR) signal pathway, which results in apoptosis of AM (92). In

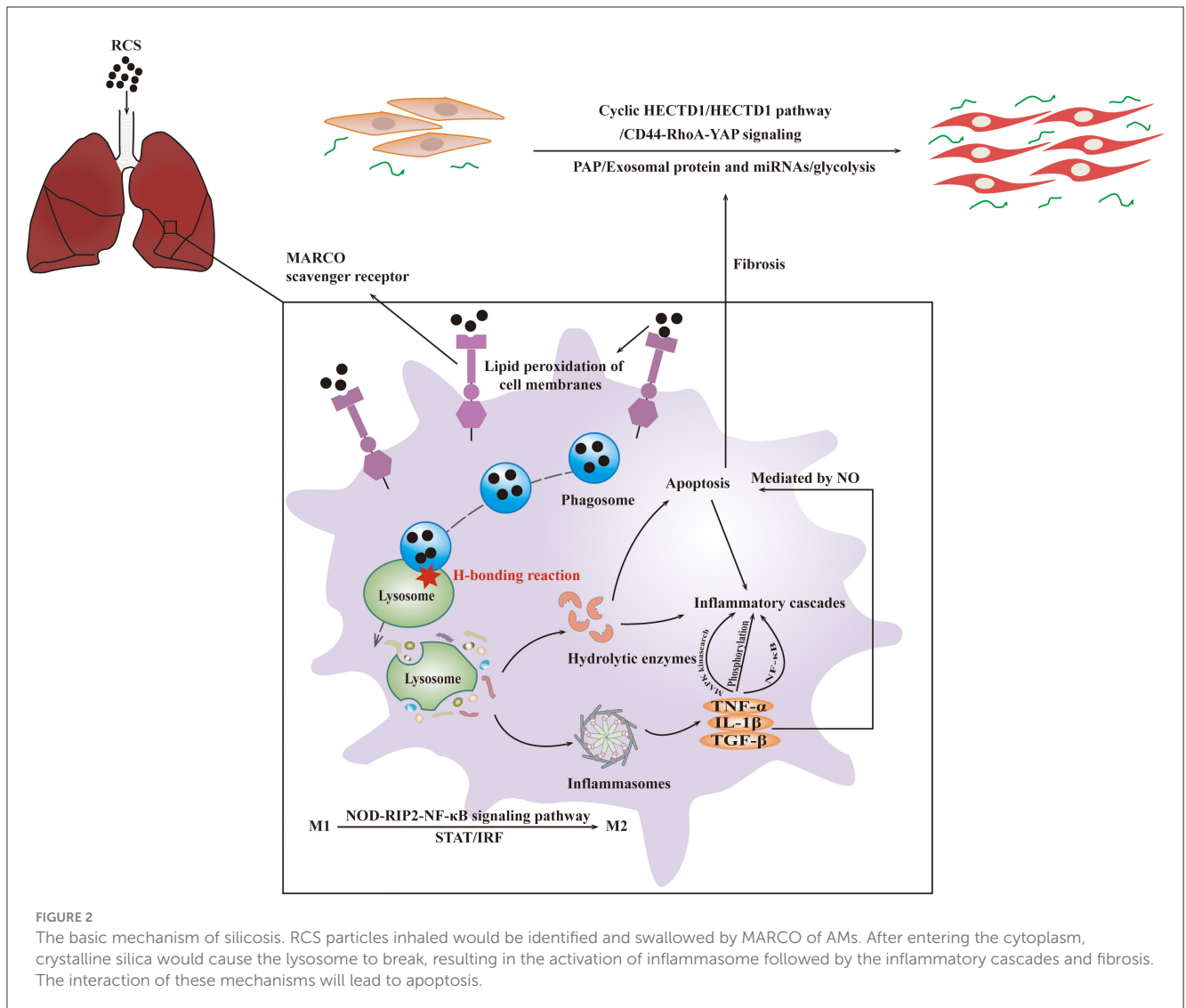
the progression of pneumoconiosis, signaling pathways and targets involved under the influence of autophagy are shown in Figure 3.

7.3 Apoptosis on the progression of pneumoconiosis

Silica-induced apoptosis exerts an inflammatory effect in the lung parenchyma and creates immunologic abnormalities in the regional lymph nodes, which could promote the progression of silicosis (93). Fas/FasL pathway may regulate the process of apoptosis. Expression of Fas ligand was reported to increase after silica inhalation, and led to the apoptosis of Fas ligand-dependent macrophage (94). Cytochrome c can help the combination of apoptotic protease activating factor-1 (APAF-1) and pro-caspase 9, resulting in the enzymatic cascade and apoptosis (95). TNFR1/Phox interaction is a crucial event in the pathogenesis of silicosis, and it inhibits the formation of mitochondrial ROS (mtROS) and reduces macrophage apoptosis (96). Up-regulation of Bax and down-regulation of Bcl-2 lead to the cleavage of caspase-9 and activation of caspase-3, respectively. Caspase-8 could activate caspase-3 through extrinsic apoptin pathway, thereby initiating a caspase-cascade and cell apoptosis (97). p53 plays a significant role in silica-induced apoptosis (98). Research showed that, after exposure to silica dust, all the levels of p53, plasminogen activator inhibitor-1, and apoptosis increased, and the levels of urokinase plasminogen activator decreased (99). TNF- α exerts an important influence on the pathogenesis of silicosis through NF- κ B, which mediates the occurrence of apoptosis and inflammation (100). ER stress could attenuate the activation of caspase-12 and protein kinase RNA-like ER kinase (PERK)/eukaryotic initiation factor 2 α /C/EBP homologous protein pathways, thus inhibiting the silica-induced apoptosis (101).

7.4 Pyroptosis on the progression of pneumoconiosis

Pyroptosis is mediated by NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome, a cytosolic multiprotein complex, which is composed of the innate immune receptor protein NLRP3, adapter protein apoptosis-associated speck-like protein containing a CARD, and inflammatory protease caspase-1. The assembled NLRP3 inflammasome can activate protease caspase-1, which promotes the release of IL-1 β and IL-18 (102). Nalp3 inflammasome is associated with dust-induced pulmonary diseases, and it was reported to play a crucial role as a main proinflammatory "danger receptor" (103). Silica-induced activation of NLRP3 inflammasome was confirmed with co-localization of Caspase-1 and NLRP3, as well as increased levels of IL-1 β and IL-18 (104). In addition, a new pathway of pyroptosis was discovered, and it was mediated by Caspase-3/-8/Gsdme pyroptotic pathways (105). Exosomal circRNA11:120406118|12040782 could facilitate NLRP3-induced macrophages pyroptosis (106), suggesting that more attention should be paid to the exosomes in terms of pathogenesis of pyroptosis. Under the influence of



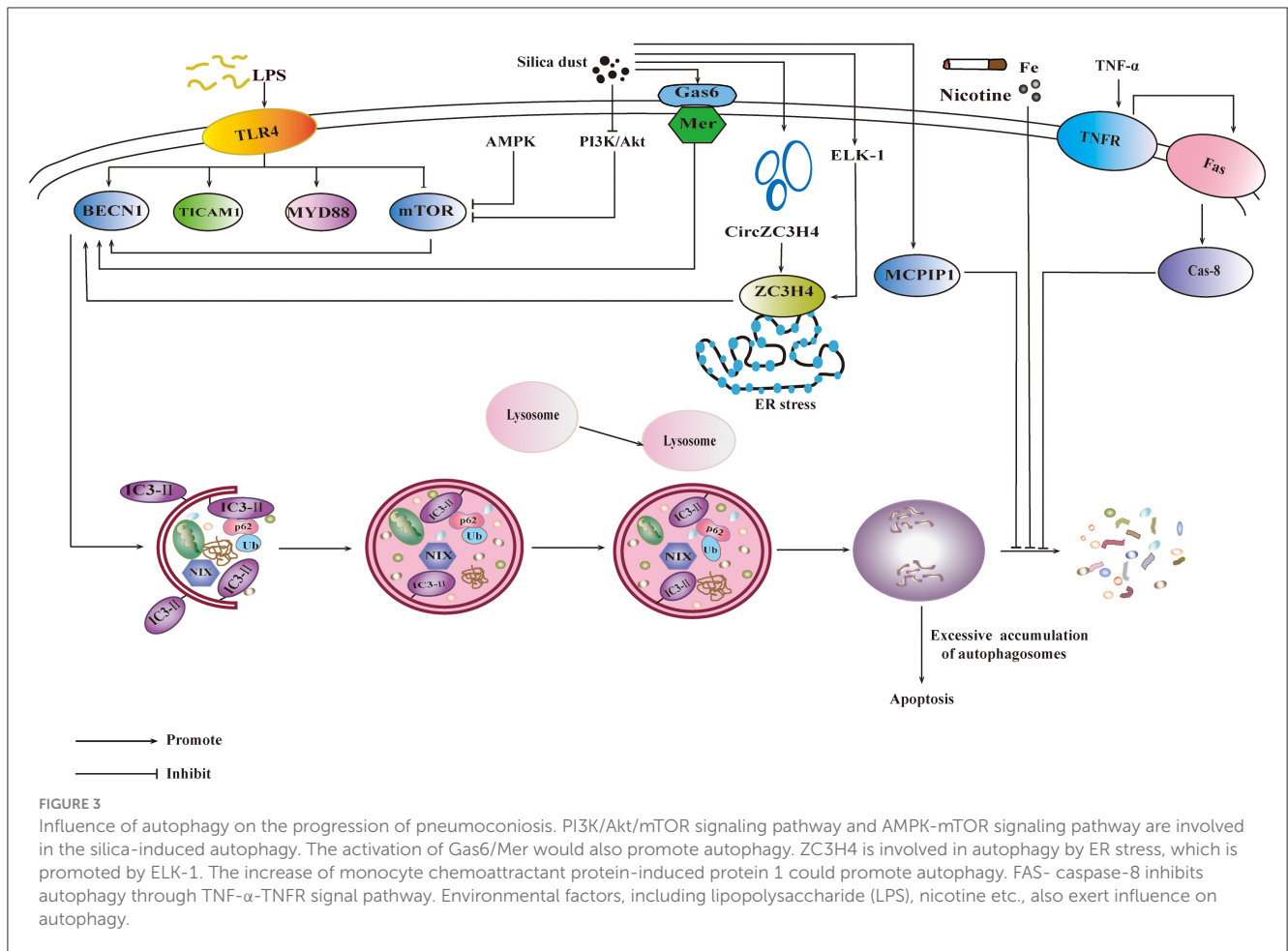
apoptosis and pyroptosis, pathways and targets involved in the progression of pneumoconiosis are shown in [Figure 4](#).

7.5 Epigenetics on the progression of pneumoconiosis

The role of epigenetics in the pathogenesis of silicosis should be studied extensively. Progression of silicosis may be caused by a combination of environmental and genetic factors. The relationship between genotype and phenotype, and the association between their correlation and disease susceptibility are very complicated due to the discrepancy in environment, lifestyle, and nutritional status (107). Recently, N-methyladenosine methylation has received considerable attention in the research on the progression of pneumoconiosis, and was found to be closely related to “phagosome,” “antigen processing and presentation,” and “apoptosis” (108). Environmental factors should be considered carefully, including smoking and bacteria.

TNF- α -308 G/A and -238A/G polymorphisms may be correlated with silicosis susceptibility, especially in Asians (109, 110). Telomerase gene variants and short telomeres may increase the susceptibility to silicosis, but do not affect the severity of the disease (111). The rs12812500 variant of the carboxypeptidase M gene may increase the susceptibility to silicosis (112). Genetic loss of Gas6 partly attenuates silica-induced autophagosomes accumulation (85), which may affect the progression of silicosis. Deficiency of RAB20 in macrophages/monocytes could promote the release of IL-1 β and the activation of NLRP3 inflammasome, resulting in injury to the lysosome (113).

A recent study showed that smoking cessation could help reduce the risk of silicosis in silica-exposed workers (114). Nicotine, an addictive component in cigarettes, may induce apoptosis by blocking AM autophagic degradation of AM (115). LPS initiates the formation of autophagosomes through a Toll-like receptor 4 (TLR4)-dependent pathway and exacerbates apoptosis in AMs (116). LPS induces autophagy and apoptosis in macrophages. With the progression of silicosis, the level of Beclin 1 increased and



the levels of the phosphorylation of MTOR, TLR4, MYD88, and TICAM1 decreased (116). A novel circRNA-SNP may increase the susceptibility to silicosis, so further investigations need to be conducted on the role of circRNAs in the progression of pneumoconiosis (117).

8 Therapeutic measures for pneumoconiosis

No cure is available for pneumoconiosis and most medical treatments can only decrease further lung damage and symptoms, underscoring the urgency of novel treatment modalities (2).

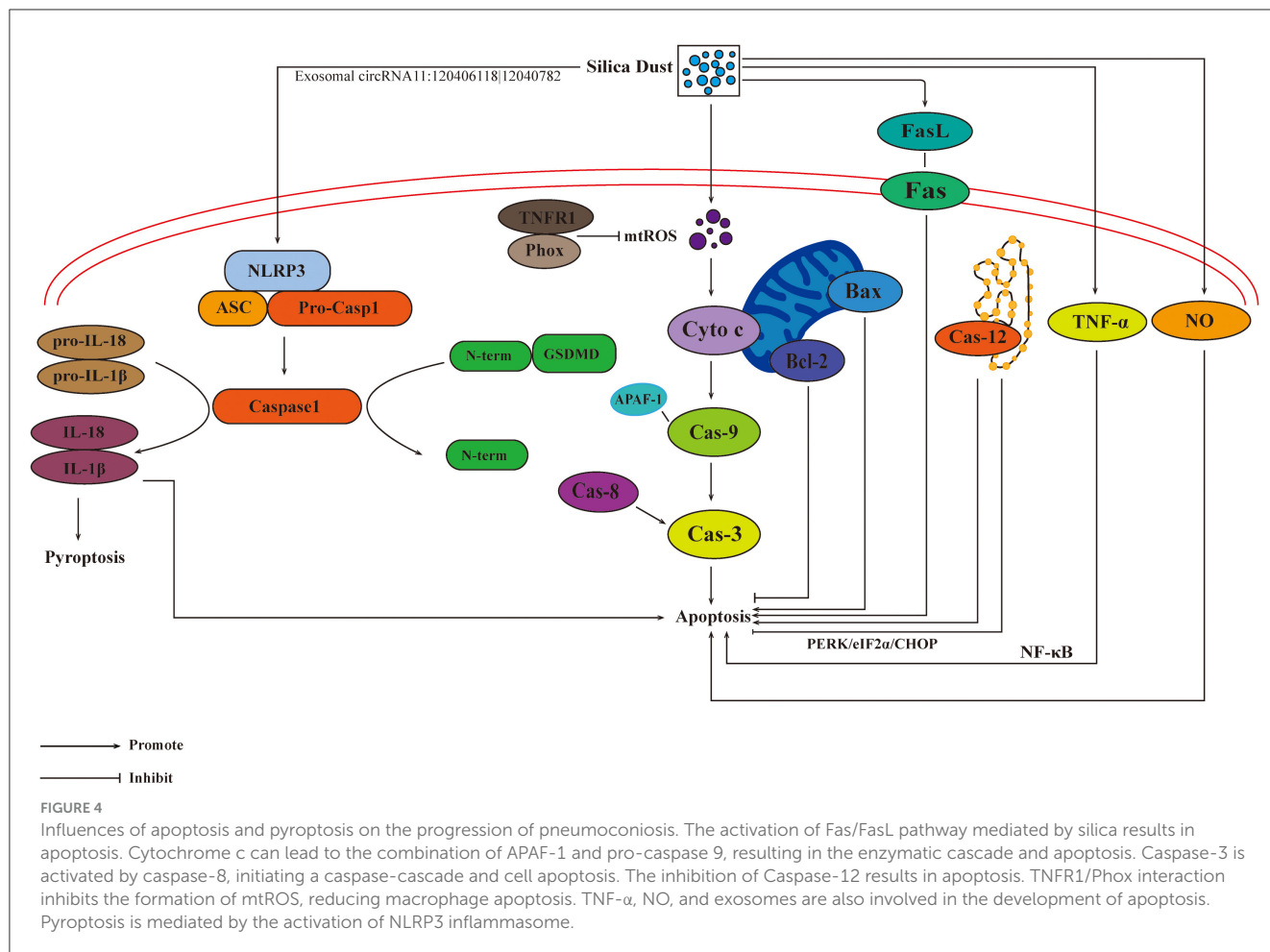
Whole lung lavage (WLL) can remove a certain amount of dust, cells, and soluble materials from the lungs, improving oxygen uptake and ventilatory efficiency in pneumoconiosis patients (118). However, negative suction pressure will cause different degrees of lung damage during WLL. Additionally, pulmonary function parameters were reported to worsen after WLL, including forced expiratory volume, residual volume, and diffusing capacity of the lungs for carbon monoxide (119).

Since there are no effective treatments available for end-stage pneumoconiosis, lung transplant is the only option for patients with fatal respiratory failure (5). However, lung transplantation

has some limitations, including donor shortage, proper selection of candidates, primary graft dysfunction, and chronic lung allograft dysfunction (120). Meanwhile, lung transplant recipients were reported to have a short median survival time of only 6–7 years (6).

8.1 Promising targets for pneumoconiosis

An increasing amount of evidence has demonstrated that the dysregulation of miRNAs may play an important role in the progression of pneumoconiosis (121). miRNAs play an important role in the progression of pneumoconiosis, and they have emerged as potent regulators of EMT and mesenchymal epithelial transition (MET). A recent study proved that miR-770-5p suppressed the activation of pulmonary fibroblasts and further inhibited silica-induced pulmonary fibrosis by targeting transforming growth factor beta receptors (TGFBR1). It was reported that transduction of TGF- β 1 signaling pathway decreased TGFBR1, and the activation of MRC-5 cells was inhibited after TGFBR1 was knocked out, while increase in the growth of these cells was observed after the overexpression of TGFBR1 (121). Spouty1 (SPRY1) is identified as the target gene of miR-7219-3p, and its knockout or overexpression could promote or inhibit fecal microbiota transplantation (FMT), respectively, via



the Ras/ERK/MAPK signaling pathway. Therefore, miR-7219-3p could be deemed a novel therapeutic target for pneumoconiosis treatment (122).

ZC3H4 participates in macrophage activation and EMT. Research has confirmed that ZC3H4 participates in the silica-induced EndoMT via ER stress and autophagy, indicating the possibility of treating pneumoconiosis by targeting ZC3H4 (89). According to a new study, A2a receptor (A2aR) could reverse EMT by mediating Wnt/ β -catenin pathway and inhibit the development of silicosis (123). Glycolytic reprogramming is an important metabolic feature of the progression of pulmonary fibrosis (124), however, the specific mechanism of glycolysis in silicosis is still unclear. A study have confirmed that N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP) treatment can inhibit glycolytic reprogramming in silica-induced lung macrophages and alleviate pulmonary fibrosis (125).

CD44-RhoA-YAP signaling is involved in mechanics-induced fibroblast activation, therefore, fibrosis in pneumoconiosis could be reversed by targeting this signaling pathway (78). Activating associated autophagy pathways, such as PI3K/Akt/mTOR and Gas6/Mer-mediated autophagy signaling pathway, is proved to have therapeutic effect on pneumoconiosis (83, 85). Fas/FasL pathway may be involved in the progression of AM apoptosis, suggesting that silicosis could be prevented or treated by inhibiting this signaling pathway (46).

Lymphatic vessels are beneficial to the removal of silica dust and the suppression of inflammation (126). Promoting the formation of lymphatic vessels is helpful in the early prevention and treatment of pneumoconiosis (126). Ginsenoside Rg1 promoted lymphatic transport in silicotic rats through vascular endothelial growth factor C/vascular endothelial growth factor receptor 3 signaling pathway, exerting a protective influence on lung burden of silica (127). Specific therapeutic targets for pneumoconiosis treatment are listed in Table 4.

8.2 Promising drugs for pneumoconiosis

Drugs used to treat other diseases, such as corticosteroids and amiodarone, could also be used in the management of pneumoconiosis (137, 138). Amiodarone, a unique antiarrhythmic agent, is effective in the treatment of a wide range of rhythm abnormalities (139). With the ability to inhibit the activity of AM and the whole lung phospholipase, amiodarone can increase the amount of phospholipids in lung cells, airways, and alveoli (138). A previous study showed that the increase in pulmonary phospholipid reduced the acute damage caused by intratracheal instillation of silica in rats, indicating that amiodarone can attenuate acute damage in lungs by increasing the content of phospholipids (138).

TABLE 4 New therapeutic targets for pneumoconiosis.

Targets	Expression level	Mechanisms	Effects	References
miR-449a	Up	Promotes autophagy	Ameliorates pulmonary fibrosis	(128)
miR-205-5p	Up	Promotes autophagy by inhibiting S-phase kinase-associated protein 2-mediated Beclin1	Ameliorates pulmonary fibrosis	(129)
miR-29b	Up	Promotes MET and by suppressing EMT	Ameliorates pulmonary fibrosis and pulmonary function	(130)
miR-770-5p	Up	Targets TGFBR1	Ameliorates pulmonary fibrosis	(121)
miR-411-3p	Up	Inhibits MRTF-A/SRF signaling	Ameliorates pulmonary fibrosis	(131)
SPRY1	Down	Inhibits the Ras/ERK/MAPK signaling pathway and reduces the expression of miR-7219-3p	Inhibits FMT and pulmonary fibrosis	(122)
miR-326	Up	Promotes autophagy by TNF superfamily14 and polypyrimidine tract-binding protein 1	Ameliorates pulmonary fibrosis	(132)
ZC3H4	Down	Regulates ER stress and autophagy	Ameliorates pulmonary fibrosis	(89, 90)
RhoGDI α	Down	Inhibits myofibroblast trans-differentiation	Ameliorates pulmonary fibrosis	(133)
IgE and Fc ϵ RI	Down	Reduce the role IgE and Fc ϵ RI play	Ameliorates pulmonary fibrosis	(134)
BCL2 binding component 3	Down	Inhibits autophagy	Ameliorates pulmonary fibrosis	(135)
Cav-1	Up	Inhibited infiltration of inflammatory cells and secretion of inflammatory factors	Ameliorates pulmonary inflammation and fibrosis	(136)
A2aR	Up	Reverses the EMT process	Ameliorates pulmonary fibrosis	(123)
CD44-RhoA-YAP signaling	Inhibit	Inhibits fibroblast activation	Ameliorates pulmonary fibrosis	(78)

In addition, some drugs extracted from natural plants with anti-inflammatory and anti-fiber properties can also be used to treat pneumoconiosis, including anti-snake venom injection (140), dihydrotanshinone I (141), and intranasal curcumin (142). Dioscin, a steroidal saponin, reduces the recruitment of fibrocytes and inhibits TNF β /Smad3 signaling, which greatly suppresses the activation of fibroblasts (143), and it could alleviate pulmonary inflammation and fibrosis by promoting autophagy and reducing apoptosis of AMs (144). Dihydroquercetin, a flavonoid compound with anti-inflammatory property, could be used for pneumoconiosis treatment because it inhibits ferritinophagy-mediated human bronchial epithelial cells ferroptosis and alleviates pulmonary fibrosis (145). Specific drugs are listed in Table 5.

8.3 Other therapies for pneumoconiosis

Systemic administration of Mesenchymal stem cells (MSCs) was reported to ameliorate lung inflammation and attenuate fibrosis in experimental silicosis, and could be used as an emerging treatment for pulmonary fibrosis (155). The group with adipose-derived MSC (AD-MSCs) transplantation showed a significant increase in Bcl-2/Bax ratio and a drastic reduction in the inflammatory response and Caspase-3 protein expression, implying that AD-MSCs may slow the development of silicosis by influencing inflammation and apoptosis (156). Bone marrow mononuclear cells significantly alleviate pulmonary inflammation and fibrosis, especially when transplanted from healthy individuals (157). However, the direct use of stem cells for therapeutic purposes has remained limited due to several factors, such as

safety and high expenditure. Magnetic targeting (MT) is regarded as a potential means of prolonging MSC retention in the lungs to improve their beneficial effects, indicating that MT could be adopted as a prospective strategy to enhance MSC therapies for pneumoconiosis (155).

Exosomes secreted from stem cells hold great therapeutic potential with the added advantage of being free from the restrictions of cell-based therapy. Exosomes derived from human umbilical cord mesenchymal stem cells (hucMSC-Exos) were reported to play a potential role in improving pulmonary fibrosis (158), since they transfer let-7i-5p to inhibit the activation of fibroblasts and then alleviate pulmonary fibrosis through the TGFBR1/Smad3 signaling pathway (159). MSC-derived extracellular vesicles (MSC-derived EVs) also have similar therapeutic potential in treating pneumoconiosis (160).

Hepatocyte growth factor (HGF) is a potential anti-inflammatory and anti-fibrotic growth factor (161), and it was reported to play a significant role in pulmonary tissue repair in adults (162). Administration of HGF protein or ectopic expression of HGF induced normal tissue repair and prevented fibrotic remodeling in animal models of pulmonary fibrosis (162). HGF inhibits fibrotic remodeling, which is mediated by multiple direct and indirect mechanisms, including the induction of cell survival, proliferation of pulmonary epithelial and endothelial cells, and reduction of myofibroblast accumulation (162), suggesting that HGF can be used to treat pneumoconiosis. HGF could also be applied to polyethyleneimine-polyethylene glycol/plasmid encoding human HGF gene/hyaluronic acid (PEG-PEI/pHGF/HA) nanoparticles carrying HGF gene through chemical synthesis; pHGF was delivered into the lungs of

TABLE 5 Prospective drugs for pneumoconiosis.

Drugs	Mechanisms	Involved signaling pathways	Effects	References
Pirfenidone	Inhibits the secretion of IL-17A Inhibits macrophage polarization Inhibits epithelial-mesenchymal transition	TGF- β 1/Smad pathway JAK2/STAT3 signaling pathway	Ameliorates pulmonary inflammation and fibrosis	(146–148)
Fostamatinib	Targets SYK	Not reported	Ameliorates pulmonary inflammation and fibrosis	(149)
Gefitinib	Targets EGFR	Not reported	Ameliorates pulmonary inflammation and fibrosis	(149)
Metformin	Activates autophagy	AMPK-mTOR signaling pathway	Attenuates pulmonary fibrosis	(84)
Ramatroban	Blocks the receptors of PGD and TXA	Not reported	Inhibits the progression of silicosis	(41)
Astragaloside IV	Reduces the expression of Collagen I, fibronectin and α -SMA	TGF- β 1/Smad signaling pathway	Attenuates pulmonary fibrosis	(140)
Intranasal curcumin	Reduces airway inflammation and structural changes	Not reported	Ameliorates lung damage	(142)
Dihydratanshinone I	Regulates the Th immune response Inhibits STAT1 and STAT3	Not reported	Ameliorates pulmonary inflammation	(141)
Carvedilol	Underlies inflammatory and fibrotic sequel	P-AKT/mTOR/TGF β 1 signaling	Ameliorates pulmonary fibrosis	(150)
Tetrandrine	Inhibits both the canonical and non-canonical NLRP3 inflammasome pathways	Canonical and non-canonical NLRP3 inflammasome pathways	Ameliorates pulmonary inflammation and fibrosis	(151)
Dioscin	Modulates innate and adaptive immune responses Reduces the recruitment of fibrocytes, protected epithelial cells Inhibits fibroblast activation Promotes autophagy Reduces apoptosis	TNF β /Smad3 signaling	Ameliorates pulmonary inflammation and fibrosis	(143, 144)
Atractylenolide III	Inhibits autophagy	mTOR-dependent signaling pathway	Alleviate the apoptosis of AMs	(152)
Tanshinone IIA	Decreases the expression of collagen I, fibronectin and α -SMA Reduces NADPH oxidase 4 expression	TGF- β 1/Smad signaling Nrf2/ARE pathway	Ameliorates pulmonary inflammation, structural damage and fibrosis	(153)
Glycyrrhizic acid	Inhibits the interaction between HMGB1 and BRG1	PI3K/Akt/mTOR pathway	Ameliorates pulmonary fibrosis	(154)

silicotic mice effectively via PEG-PEI(HA), and it resulted in a decrease in inflammation and collagen deposition in the lungs. Therefore, gene therapy with PEG-PEI/pHGF/HA nanoparticles is a promising strategy for the treatment of silicosis, and it would provide research foundation and novel ideas for the treatment of silicosis (163). The combination of MSC and HGF has been reported to have good therapeutic effect on some pneumoconiosis patients (164).

Nanotechnology can be integrated with existing drugs for the treatment of pneumoconiosis or be applied to the development of new therapies, which will make drugs more effective and reduce the undesirable side effects, and the therapeutic goals can be better achieved. Compared with stand-alone drugs in traditional respiratory therapy, the integration of drugs and different nanostructures showed a better drug bioavailability, transport, and delivery (165). A study reported that fullerene nanoparticles (FNs) could effectively inhibit the activation of NLRP3 inflammasome, which could prevent the secretion of mature IL-1 β and neutrophil influx due to its superior ROS scavenging capability. Importantly, FNs did not cause any obvious toxicity

after pulmonary administration (166). New nanotechnologies such as FNs will be a boon to the treatment of pneumoconiosis in the future.

9 Prospects of pneumoconiosis

Further research needs to be conducted on the pathogenesis of pneumoconiosis to find novel and accurate targets for diagnosis and to develop new therapeutic approaches. Recently, increasing research has revealed that autophagy, apoptosis and pyroptosis are involved in the development of pneumoconiosis to a certain extent (166). The occurrence of pneumoconiosis is dependent on the interaction between three above-mentioned phenomena (167), and molecules and signaling pathways involved in these processes can be used as diagnostic and therapeutic targets for pneumoconiosis. Additionally, the mechanism of pneumoconiosis should be considered from the perspective of the interplay between genetic and environmental factors (107). More environmental factors and relevant genes are expected to be discovered in future studies,

which would help to explain the pathogenesis of pneumoconiosis more clearly. As carriers, exosomes could transport specific cargoes such as nucleic acids, lipids and proteins, and promote biological process and idiopathic pulmonary fibrosis (82). Further research on the role of exosomes in pathogenesis of pneumoconiosis would uncover novel promising biomarkers, therapeutic targets, and relevant drugs.

Developing effective specific models such as pre-clinical and human organoid-based models is significant for further exploration on the mechanisms of pneumoconiosis (36). Like any other controllable model organisms, complex patient-derived mannequin systems will consequently become powerful research tools for understanding human physiology and disease development (168). Besides, it is equally important to apply various new research techniques to the field of pneumoconiosis because a single technique alone fails to explain the mechanism of this disease in most of the cases. For example, integrative omics plays a key role in the prediction and early diagnosis of pneumoconiosis as well as in the treatment and prognosis (169). Multi-omics approach was used and it was found that mA methylation played an essential role in the occurrence of silicosis. Multi-omics approach could be used as a novel and viable strategy for the prevention and treatment of silicosis. These approaches have paved the way for clarifying the epigenetic mechanisms underlying the pathogenesis of silicosis (108). Rapid development of integrative omics such as genomics, transcriptomics, proteomics, and metabolomics has revealed the differences among individuals indicating that personalized medicine has great application prospect. Personalized medicine would provide specific individuals with interventions for their diseases, and the treatments can be tailored to their nuanced needs caused by the differences in the levels of molecule, physiology, environmental exposure, and behavior.

New lung scanning methods, including HRCT, EIT, and magneto pneumography, have improved the reliability of diagnosis of pneumoconiosis, making early diagnosis of pneumoconiosis possible (58, 59, 62). Standardized techniques, coordination, and consensus should be adopted to promote the clinical application of these imaging methods (60). AI, a hot topic in medical imaging, is a promising method in the diagnosis of pneumoconiosis, for it can develop diagnostic algorithms in an innovative way with the advantage of evaluating multiple issues rapidly (63). In addition, it is important to find novel biomarkers for early and accurate diagnosis of pneumoconiosis (2). Existing methods, such as WLL, cause damage to human body, though they can alleviate the progression of pneumoconiosis (119). Several drugs with anti-inflammatory and anti-fiber properties have been found useful in the treatment of pneumoconiosis. Researchers are expected to develop more new drugs that can treat pneumoconiosis effectively (88). Being adult stem cells, MSCs have shown promising results in the treatment of pneumoconiosis (156), with strong differentiation ability and immune regulation function (170). Importantly, the secretory factors produced by MSCs play critical roles in tissue repair, which support both engraftment and trophic functions (autocrine and paracrine) (170). With these features, MSCs have been increasingly utilized in clinical trials for cell replacement and immune suppression, and they are considered promising in

the treatment of pneumoconiosis. It is worth noting that HGF's anti-inflammatory and anti-fibrotic attributes make it possible to treat pneumoconiosis and alleviate its progression (162). The combination of HGF with nanotechnology or MSCs will be of much significance to the treatment of pneumoconiosis (163, 164).

Author contributions

XH: Methodology, Writing – original draft, Funding acquisition. ZW: Methodology, Writing – original draft. XJ: Methodology, Writing – review & editing. CW: Methodology, Writing – review & editing. LD: Formal analysis, Methodology, Writing – review & editing. YL: Writing – review & editing. RL: Writing – review & editing. JN: Formal analysis, Resources, Writing – review & editing. YS: Methodology, Funding acquisition, Writing – review & editing. XQ: Conceptualization, Formal analysis, Funding acquisition, Methodology, Supervision, Project administration, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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