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ADVANCING THERAPEUTIC STRATEGIES FOR SILICOSIS CHALLENGES AND FUTURE PERSPECTIVES

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Abstract. Silicosis is a progressive occupational lung disease caused by prolonged inhalation of crystalline silica particles and remains a significant global public health concern. Despite advances in occupational safety measures, the disease continues to affect workers in mining, construction, quarrying, and artificial stone industries. The pathogenesis of silicosis involves a complex interaction between oxidative stress, chronic inflammation, NLRP3 inflammasome activation, immune dysregulation, and pulmonary fibrosis. Currently, no definitive curative treatment is available, and existing therapeutic approaches are primarily aimed at slowing disease progression and improving quality of life. This review summarizes the major pathogenic mechanisms underlying silicosis and evaluates current and emerging therapeutic strategies, including antifibrotic agents, anti-cytokine therapies, antioxidants, inflammasome inhibitors, autophagy modulators, stem cell-based therapies, extracellular vesicles, and molecular-targeted interventions. Recent experimental and clinical findings suggest that targeting multiple pathogenic pathways may provide improved therapeutic outcomes. Future advances in regenerative medicine and precision therapeutics may contribute to the development of more effective treatment strategies for patients with silicosis.

Keywords: Silicosis; Pulmonary fibrosis; Oxidative stress; NLRP3 inflammasome; Antifibrotic therapy; Mesenchymal stem cells; Targeted therapy.

Introduction

Silicosis is one of the most common occupational pneumoconioses caused by prolonged inhalation of respirable crystalline silica particles. Silica, also known as silicon dioxide (SiO_2), is naturally abundant in the Earth's crust and is widely encountered in mining, quarrying, sandblasting, construction, and artificial stone processing industries. Continuous exposure to crystalline silica dust can result in progressive lung injury characterized by chronic inflammation, formation of silicotic nodules, and irreversible pulmonary fibrosis.

Depending on the intensity and duration of exposure, silicosis is generally classified into chronic, accelerated, and acute forms. Chronic silicosis develops after prolonged exposure to relatively low concentrations of silica dust, whereas accelerated and acute silicosis occur following higher exposure levels over shorter periods. The disease may initially remain asymptomatic; however, progressive deterioration of pulmonary function can lead to dyspnea, chronic cough, respiratory insufficiency, and increased susceptibility to tuberculosis and other pulmonary complications.

Despite significant advances in occupational safety and dust control technologies, silicosis continues to represent a major global health challenge. The absence of a definitive curative treatment and the irreversible nature of pulmonary fibrosis highlight the urgent need for novel therapeutic approaches. Therefore, understanding the underlying pathogenic mechanisms and

evaluating emerging treatment strategies are essential for improving clinical outcomes in patients with silicosis.

Pathomechanisms of Silicosis

Silicosis is a progressive occupational lung disease caused by the long-term inhalation of respirable crystalline silica particles. The pathogenesis of silicosis involves a complex interaction between inflammatory responses, oxidative stress, immune dysregulation, and fibrotic remodeling of lung tissue. Although significant progress has been made in understanding the disease, the exact mechanisms responsible for its initiation and progression remain incompletely understood. Current evidence suggests that multiple interconnected biological processes contribute to the development of pulmonary fibrosis and irreversible lung damage.

The major pathogenic mechanisms involved in silicosis include:

- Inhalation and deposition of crystalline silica particles in the distal airways and alveolar regions of the lungs.
- Recognition and phagocytosis of silica particles by alveolar macrophages through scavenger receptors and pattern-recognition receptors.
- Direct cytotoxic effects of silica on macrophages, resulting in cellular injury, apoptosis, and pyroptosis.
- Generation of excessive reactive oxygen species (ROS) and reactive nitrogen species (RNS), leading to oxidative stress and cellular damage.
- Activation of intracellular signaling pathways, including nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways.
- Rupture of lysosomal membranes following silica uptake and release of proteolytic enzymes into the cytoplasm.
- Activation of the NLRP3 inflammasome complex and subsequent production of pro-inflammatory cytokines.
- Increased secretion of inflammatory mediators such as interleukin-1β (IL-1β), interleukin-18 (IL-18), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α).
- Recruitment and accumulation of inflammatory cells, including neutrophils, monocytes, and lymphocytes, within pulmonary tissue.
- Persistent chronic inflammation resulting in continuous tissue injury and impaired repair mechanisms.
- Stimulation of fibroblast proliferation and differentiation into collagen-producing myofibroblasts.
- Excessive synthesis and deposition of extracellular matrix proteins, including collagen and fibronectin.
- Formation of silicotic nodules and progressive pulmonary fibrosis.
- Reduction of pulmonary elasticity, impairment of gas exchange, and gradual decline in respiratory function.

Among these mechanisms, chronic inflammation and fibrosis are considered the most important determinants of disease progression. Continuous exposure to silica particles creates a vicious cycle in which macrophage injury, cytokine release, oxidative stress, and fibroblast activation reinforce one another. Consequently, normal lung architecture is progressively replaced by fibrotic tissue, leading to irreversible structural and functional impairment.

Furthermore, recent studies have demonstrated that immune dysregulation plays a significant role in silicosis development. Alterations in both innate and adaptive immune responses contribute to prolonged inflammation, autoimmune reactions, and enhanced fibrogenesis. The interaction

between inflammatory pathways and fibrotic signaling molecules, particularly transforming growth factor-beta (TGF-β), is regarded as a critical factor in the progression of the disease.

A comprehensive understanding of these pathogenic mechanisms provides the scientific basis for the development of modern therapeutic strategies. Many current and emerging treatment approaches aim to suppress inflammation, reduce oxidative stress, inhibit inflammasome activation, and prevent pulmonary fibrosis, thereby slowing disease progression and improving patient outcomes.

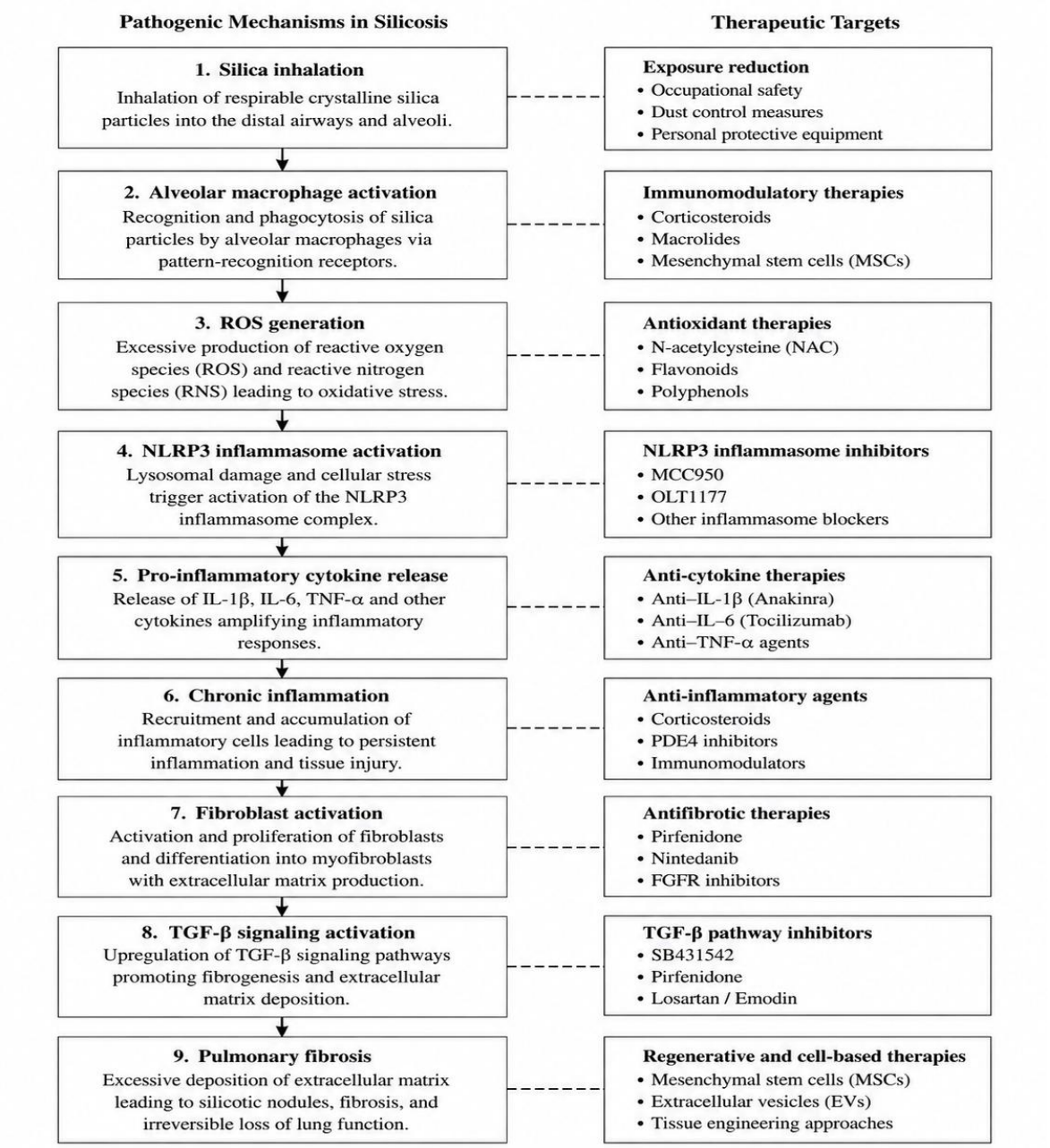


Figure 1. Mechanisms of Silica-Induced Lung Injury and Corresponding Therapeutic Targets

Figure 1 summarizes the major pathogenic events involved in silicosis progression and highlights the corresponding therapeutic targets currently being investigated. The diagram

illustrates how silica-induced oxidative stress, inflammasome activation, cytokine release, and fibrotic signaling pathways contribute to pulmonary fibrosis and identifies potential intervention points for emerging therapies.

Current and emerging therapeutic strategies for silicosis

Silicosis remains a major occupational health challenge worldwide due to its progressive course and the lack of a definitive curative treatment. Current therapeutic interventions are primarily directed toward controlling inflammation, reducing oxidative stress, preventing excessive fibrotic remodeling, and preserving pulmonary function. Advances in the understanding of disease pathogenesis have facilitated the identification of several therapeutic targets, leading to the development of both conventional and emerging treatment approaches.

Despite advances in the understanding of silicosis pathogenesis, no definitive curative treatment has yet been established. Therefore, current clinical management remains largely supportive and focuses on symptom relief, slowing disease progression, and improving patients' quality of life. Whole-lung lavage has been used in selected patients, particularly during the early stages of the disease, where it may improve respiratory symptoms and functional capacity. In severe and end-stage cases, lung transplantation remains the only effective therapeutic option capable of significantly extending survival, although its application is limited by donor availability, high cost, and post-transplant complications.

Recent studies have demonstrated that multiple pathological pathways involved in silicosis progression can be targeted therapeutically. These include chronic inflammation, cytokine-mediated signaling, oxidative stress, inflammasome activation, autophagy dysfunction, and fibroblast-mediated extracellular matrix deposition. Consequently, a broad range of pharmacological and biological interventions have been investigated to interrupt these pathogenic mechanisms and mitigate lung injury. In addition to conventional management strategies, several pharmacological and biological therapies have demonstrated promising results in experimental and clinical studies. Antifibrotic agents such as pirfenidone and nintedanib have shown the ability to reduce fibrosis progression, while tetrandrine has been reported to suppress pulmonary inflammation and improve lung function. Furthermore, anti-cytokine therapies, antioxidants, stem cell-based interventions, extracellular vesicles, and molecular-targeted therapies are being actively investigated as potential approaches for modifying disease progression and improving long-term outcomes.

Table 1. Current and emerging therapeutic strategies for silicosis

Therapeutic category	Representative agents	Primary therapeutic target	Expected clinical effect	Research status
Antifibrotic agents	Pirfenidone, Nintedanib	TGF-β signaling, fibroblast activation	Reduction of fibrosis progression and collagen deposition	Preclinical and clinical evidence
Anti-cytokine therapy	Anakinra, Anti-IL-17, Anti-IL-9, Infliximab	IL-1β, IL-17, TNF-α pathways	Suppression of chronic inflammation	Experimental/early clinical
Inflammasome inhibitors	NLRP3 and Caspase-1 inhibitors	Inflammasome activation	Reduction of inflammatory mediator release	Preclinical

Autophagy modulators	Imipramine, Dioscin, Rapamycin, Trehalose, Atractylenolide III	Autophagy–lysosomal pathway	Improved cellular homeostasis and reduced fibrosis	Preclinical
Antioxidants	N-acetylcysteine, Flunisolide	Oxidative stress and ROS production	Protection against cellular injury	Preclinical-clinical
Corticosteroids	Dexamethasone and related agents	Inflammatory signaling pathways	Short-term reduction of inflammation	Limited evidence
Endogenous glucocorticoid regulators	Annexin A1	Resolution of inflammation	Modulation of immune responses	Experimental
cAMP-enhancing agents	Roflumilast, Tadalafil, Sildenafil	cAMP signaling pathways	Anti-inflammatory and antifibrotic effects	Preclinical
TGF-β pathway inhibitors	Emodin, Ponatinib	Profibrotic signaling	Suppression of fibroblast activation	Preclinical
Other anti-inflammatory agents	Rupatadine, Piroxicam, Nicorandil, Hesperetin	Multiple inflammatory pathways	Reduction of fibrosis and oxidative injury	Preclinical
Gene-based therapy	MicroRNA-targeted approaches	Gene expression regulation	Precision control of fibrotic pathways	Experimental
Cell-based therapy	Mesenchymal stem cells (MSCs)	Tissue repair and immunomodulation	Lung regeneration and fibrosis attenuation	Preclinical-early clinical
Extracellular vesicle therapy	MSC-derived extracellular vesicles	Cell-to-cell signaling	Enhanced tissue repair and immune regulation	Experimental

As summarized in Table 1, current therapeutic strategies for silicosis target multiple pathogenic pathways, including inflammation, oxidative stress, inflammasome activation, and pulmonary fibrosis. Although several approaches have demonstrated promising results in experimental studies, further clinical investigations are required to establish their efficacy and safety in patients with silicosis.

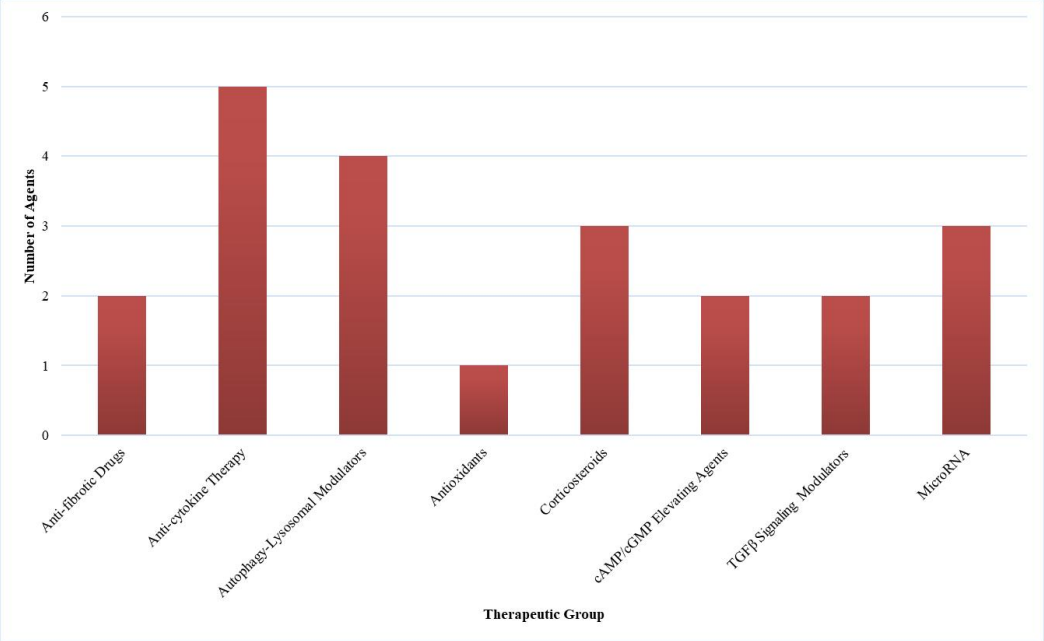


Figure 2. Distribution of Therapeutic agents among current and emerging treatment strategies for silicosis

Figure 2 illustrates the distribution of therapeutic agents investigated for silicosis treatment according to their primary mechanism of action. Anti-cytokine therapies and autophagy–lysosomal modulators constitute the largest groups of emerging therapeutic approaches, reflecting the growing interest in targeting inflammatory and cellular regulatory pathways. In contrast, antioxidant and antifibrotic strategies include a smaller number of agents but remain among the most clinically advanced therapeutic options.

The therapeutic approaches currently under investigation encompass antifibrotic agents, anti-inflammatory and anti-cytokine therapies, antioxidants, modulators of autophagy and lysosomal activity, corticosteroids, stem cell-based therapies, and molecularly targeted interventions. Antifibrotic drugs have shown potential in suppressing fibroblast activation and reducing collagen accumulation, thereby slowing the progression of pulmonary fibrosis. Similarly, therapies targeting inflammatory cytokines and signaling molecules have demonstrated the ability to attenuate chronic inflammatory responses and limit tissue damage.

In addition, increasing attention has been directed toward therapies aimed at reducing oxidative stress and inhibiting inflammasome activation, both of which are recognized as central contributors to silica-induced lung injury. Experimental evidence suggests that modulation of these pathways may decrease cellular damage, suppress inflammatory mediator production, and improve pulmonary tissue integrity. Furthermore, regulation of autophagy-related mechanisms has emerged as a promising strategy for restoring cellular homeostasis and preventing the accumulation of damaged intracellular components.

The rapid development of regenerative medicine has also opened new perspectives for silicosis treatment. Mesenchymal stem cells and extracellular vesicle-based therapies have demonstrated immunomodulatory and tissue-repair capabilities in preclinical studies. These biological approaches may promote regeneration of damaged lung tissue while simultaneously reducing inflammation and fibrosis.

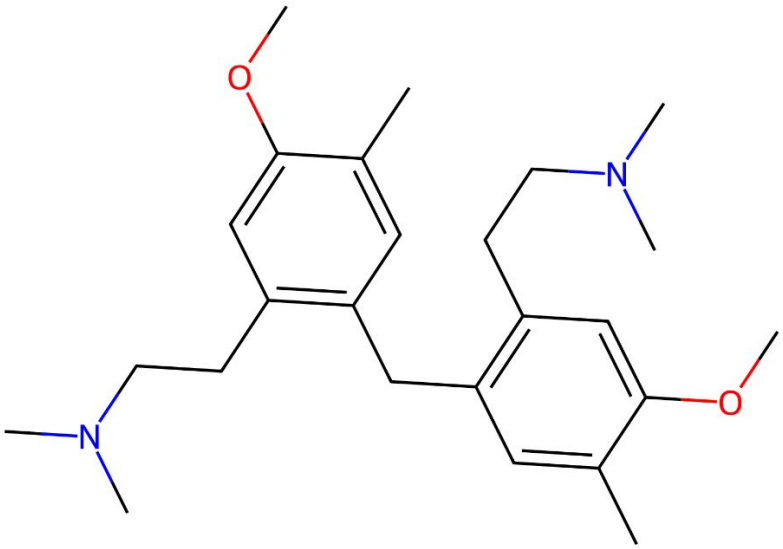


Figure 3. Chemical structure of Compound 46-107, one of the early experimental agents investigated for the treatment of silicosis.

Early experimental investigations of silicosis therapy focused on compounds capable of protecting macrophages from silica-induced cytotoxicity. Among these agents, Compound 46-107 demonstrated the ability to inhibit the formation of silicotic nodules in animal models. Although it was never introduced into clinical practice, studies involving this compound provided important insights into the pharmacological modulation of silica-induced cellular injury and contributed to the development of subsequent therapeutic approaches.

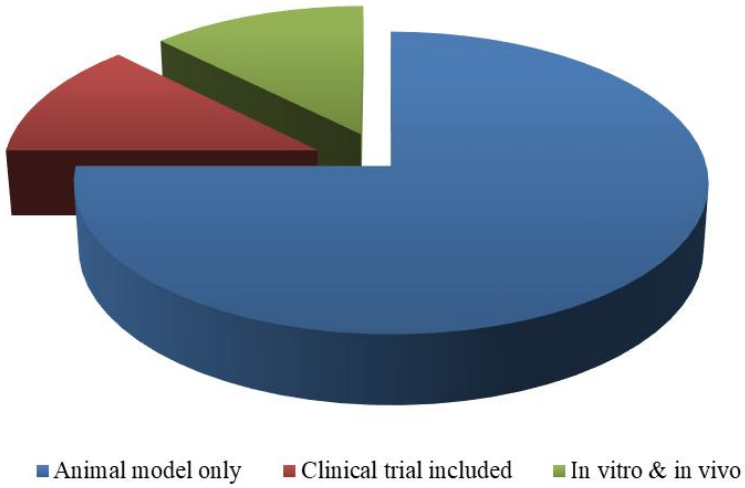


Figure 4. Distribution of Silicosis studies according to experimental design

Figure 4 illustrates the distribution of studies included in this review according to their experimental design. Animal model studies constituted the majority of publications, followed by clinical investigations and combined in vitro/in vivo studies. Moreover, advances in molecular and

translational medicine have enabled the identification of novel therapeutic targets, including transforming growth factor-beta (TGF-β), NLRP3 inflammasome signaling, cyclic adenosine monophosphate (cAMP)-associated pathways, and microRNA-regulated networks. Targeting these mechanisms may offer more selective and effective therapeutic options and contribute to the development of personalized treatment strategies for patients with silicosis.

Although many of these interventions have shown encouraging results in experimental and early clinical studies, further large-scale investigations are required to establish their long-term safety, efficacy, and clinical applicability. Nevertheless, the integration of antifibrotic, anti-inflammatory, antioxidant, regenerative, and molecularly targeted therapies represents a promising direction for improving disease management and patient outcomes in silicosis.

Future perspectives and challenges

Recent advances in understanding the molecular and cellular mechanisms of silicosis have created new opportunities for the development of targeted therapeutic strategies. Increasing evidence suggests that key pathogenic pathways, including oxidative stress, NLRP3 inflammasome activation, pro-inflammatory cytokine release, fibroblast proliferation, and TGF-β-mediated fibrogenesis, represent promising targets for disease-modifying interventions. Experimental studies have demonstrated that modulation of these pathways may attenuate inflammation, reduce extracellular matrix deposition, and slow the progression of pulmonary fibrosis. In particular, NLRP3 inflammasome inhibitors, microRNA-based therapies, and agents regulating autophagy have emerged as potential approaches capable of interrupting critical mechanisms involved in silica-induced lung injury.

In addition to molecular-targeted therapies, regenerative medicine has gained considerable attention as a potential future treatment strategy. Mesenchymal stem cells and MSC-derived extracellular vesicles have demonstrated immunomodulatory, anti-inflammatory, and tissue-repair properties in preclinical models. These biological approaches may contribute to the restoration of damaged pulmonary tissue while simultaneously suppressing chronic inflammatory responses. Furthermore, advances in precision medicine may enable the identification of patient-specific molecular signatures, facilitating individualized therapeutic interventions and improving treatment efficacy.

Despite these promising developments, several challenges continue to limit clinical translation. Most available evidence originates from experimental animal models, whereas large-scale randomized clinical trials remain scarce. Differences in disease progression, exposure characteristics, and individual susceptibility further complicate the evaluation of therapeutic efficacy. In addition, long-term safety, optimal dosing regimens, delivery systems, and potential adverse effects of emerging therapies require comprehensive investigation before routine clinical implementation.

Table 2. Emerging therapeutic targets and future research directions in silicosis

Therapeutic Target	Mechanism	Potential Benefit	Development Stage
NLRP3 inflammasome	Inflammation suppression	Reduced cytokine release	Preclinical
TGF-β	Antifibrotic effect	Reduced fibrosis	Preclinical
MicroRNA	Gene regulation	Precision therapy	Experimental
MSC-derived EVs	Tissue	Lung repair	Experimental

	regeneration		
Autophagy pathways	Cellular homeostasis	Reduced cell injury	Preclinical

As summarized in Table 2, future therapeutic development in silicosis is increasingly focused on molecular and cellular pathways involved in inflammation, fibrosis, immune regulation, and tissue regeneration. These targets represent promising opportunities for the development of personalized and disease-modifying therapies; however, further translational and clinical studies are required before their routine implementation in clinical practice.

Future research should therefore focus on integrating molecular, cellular, and clinical approaches to develop effective disease-modifying therapies. A deeper understanding of the interactions among inflammation, immune dysregulation, oxidative stress, and fibrosis may facilitate the identification of novel therapeutic targets and biomarkers. Continued progress in translational research, combined with advances in regenerative medicine and precision therapeutics, is expected to improve clinical outcomes and provide new hope for patients affected by silicosis.

Conclusion

Silicosis remains one of the most significant occupational respiratory diseases worldwide, characterized by progressive pulmonary fibrosis, chronic inflammation, and irreversible impairment of lung function. This review demonstrates that the pathogenesis of silicosis involves a complex interaction between oxidative stress, NLRP3 inflammasome activation, cytokine-mediated inflammatory responses, immune dysregulation, and fibrotic remodeling of lung tissue. Although current therapeutic options are primarily supportive and unable to reverse established fibrosis, recent advances in understanding the molecular mechanisms of disease progression have led to the identification of numerous promising therapeutic targets. Antifibrotic agents, anti-cytokine therapies, antioxidants, inflammasome inhibitors, autophagy modulators, and regenerative medicine approaches have shown encouraging results in experimental and early clinical studies.

Future progress in silicosis management will likely depend on the development of multimodal and personalized treatment strategies capable of simultaneously targeting multiple pathogenic pathways. Emerging approaches involving mesenchymal stem cells, extracellular vesicles, gene-based interventions, and precision molecular therapies offer new opportunities for reducing inflammation, limiting fibrosis, and promoting lung tissue repair. However, further large-scale clinical trials are required to confirm their long-term safety, efficacy, and clinical applicability. Continued integration of molecular research, translational medicine, and regenerative technologies may contribute to the development of effective disease-modifying therapies and improve the prognosis and quality of life of patients affected by silicosis.

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