Toward targeted treatments for silicosis

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Purpose of review
There has been a rapid increase in silicosis cases, particularly related to artificial stone. The key to management is avoidance of silica exposure. Despite this, many develop progressive disease and there are no routinely recommended treatments. This review provides a summary of the literature pertaining to pharmacological therapies for silicosis and examines the plausibility of success of such treatments given the disease pathogenesis.

Recent findings
In-vitro and in-vivo models demonstrate potential efficacy for drugs, which target inflammasomes, cytokines, effector cells, fibrosis, autophagy, and oxidation.

Summary
There is some evidence for potential therapeutic targets in silicosis but limited translation into human studies. Treatment of silicosis likely requires a multimodal approach, and there is considerable cross-talk between pathways; agents that modulate both inflammation, fibrosis, autophagy, and ROS production are likely to be most efficacious.

Keywords
pharmacology, silicosis, therapeutics

INTRODUCTION

Silicosis is an occupational interstitial lung disease caused by the inhalation of respirable crystalline silica (RCS) particles. Silicosis remains a global issue as in 2017, the Global Burden of Disease study identified 23 695 incident cases of silicosis [1], with the highest rate of new cases reported in the East Asia region. Considering millions of workers worldwide are exposed to occupational RCS, the reported cases are likely to be a major underestimation of the actual number of affected workers. In recent years, there has been a rapid increase in cases of silicosis identified in high-income and middle-income countries such as Australia [2], Spain [3], Israel [4], and India [5], primarily related to the popularity of high silica content artificial stone used to fabricate domestic benchtops.

Direct cytotoxic effects of silica and stimulation of unresolving inflammation and fibrosis result in parenchymal damage and a varied spectrum of disease. Silicosis can be slowly progressive, such as that of chronic silicosis, or rapidly progressive, such as in those who develop accelerated silicosis. Risk factors for increased disease progression include higher cumulative exposure, type of exposure (e.g. exposure to artificial stone), lower lung function, larger size and extent of lung opacities, and elevated serum angiotensin-converting enzyme (ACE) levels [6,7]. Patients with silicosis may be asymptomatic or develop breathlessness, cough, chest pain, and respiratory failure.

The key to management of silicosis is the avoidance of further exposure to RCS, however, even following exposure cessation, many will exhibit progressive disease. Despite the increasing prevalence and devastating impact of silicosis, there are no routinely recommended treatments in clinical practice beyond lung transplantation for end-stage disease.

This review provides a summary of the literature pertaining to pharmacological therapies for silicosis and examines the plausibility of success of such

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KEY POINTS

- There has been a worldwide increase in silicosis cases, and there are no routinely recommended treatments.
- In-vitro and in-vivo models demonstrate potential efficacy for drugs, which target inflammasomes, cytokines, effector cells, fibrosis, autophagy, and oxidation.
- Therapies which target targets IL-1, IL-17, TNF, and TGF and has anti-inflammatory and antifibrotic effects with the least chance of unwanted side effects may be most effective.

treatments given the disease pathogenesis. It includes currently available drugs, repurposed drugs, and treatments under development. It includes evidence derived from in-vitro and animal models and indirect evidence from similar lung conditions such as sarcoidosis and idiopathic pulmonary fibrosis (IPF). It does not include Chinese Medicine-derived therapies, and readers are directed to an excellent review by Adamcakova and Mokra [8] for a review of this literature, nor does it include nonpharmacological treatments such as whole lung lavage or lung transplantation. In summarizing the current available pharmacological evidence, this review provides a call to arms to urgently progress possible effective therapies to human trials to find efficacious management strategies for these patients.

PATHOGENESIS OF SILICOSIS

Determination of the most effective treatments for silicosis requires an understanding of the pathways that contribute to the pathogenesis of the disease. Silica is a naturally occurring particle found in quartz. Exposure to respirable ($<10\,\mu m$ in size) crystalline silica occurs most commonly in occupations that involve disturbing the earth's crust (mining) or the processing of quartz-containing materials (mining production, tunnelling, abrasive blasting, processing artificial stone). There are multiple mechanisms by which lung injury occurs. Inhaled silica particles reach the distal bronchioles and alveoli of the lung, where they are engulfed by resident alveolar macrophages and endocytosed by epithelial cells lining the airways, which are unable to clear the silica, leading to aberrant inflammation and injury. Scavenger receptors and macrophage receptors with collagenous structures (MARCO) recognize and stimulate the phagocytosis of silica by macrophages [9]. In an attempt at repair, granulomas and inflammatory cells aggregate to form silicotic nodules. Ongoing inflammation causes perpetual lung injury, resulting in the coalescence of silicotic nodules, fibrosis or scarring, and the obliteration of functional lung parenchyma [10,11].

THE NLRP3 INFLAMMASOME IS A MASTER REGULATOR OF INFLAMMATION

Once inside cells such as macrophages and epithelial cells, silica particles activate the nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (NLRP3) inflammasome – a cytoplasmic multimeric protein complex of the innate immune system, which induces further inflammation [12] (Fig. 1). Genetic polymorphisms in NLRP3 and caspase-1 have been associated with increased susceptibility to silicosis [13]. NLRP1 is another member of the NOD-like receptor (NLR) family capable of forming active inflammasome complexes [14]. Inflammasomes are activated by a range of mediators from infection, tissue damage, and cellular stress. Following activation, caspase-1 cleaves pro-IL-1β and pro-IL-18 into their mature and bioactive forms, IL-1β and IL-18, respectively. Additionally, caspase-1 activation also leads to cleavage of gasdermin D (GSDMD). Active N-terminal GSDMD subunits insert into the lipid membrane and oligomerize to form a transmembrane pore, which facilitates the release of IL-1β and IL-18 [15–17] and results in pyroptosis, an inflammatory form of cell death.

THERAPEUTIC TARGETING INFLAMMASOME RESPONSES

Studies utilizing gene-deficient mice have demonstrated a major role for inflammasomes in promoting chronic inflammation and the development of fibrosis in silicosis. These include studies in *Asc*$^{-/-}$, *Nlrp3*$^{-/-}$, *Gsdmd*$^{-/-}$, and *Gsdme*$^{-/-}$ mice [18–21]. Interestingly, genetic deficiency of caspase-1 or caspase-1 inhibitor treatment has been shown to not largely attenuate silicosis disease [21]. Small-molecule inhibitors of inflammasomes are not currently clinically available. The strategy of targeting inflammasomes directly provides the opportunity to collectively limit IL-1β and IL-18 maturation and pyroptosis (Fig. 1). Direct targeting of NLRP3 and/or NLRP1 inflammasomes with inhibitors may offer advantages over current anti-IL-1 therapies (e.g. anakinra and canakinumab), which have been associated with the development of autoantibodies and an increased risk of infections [22,23].

MCC950 is a compound that inhibits NLRP3-mediated oligomerization and subsequent inflammasome assembly, resulting in inhibition of IL-1β [24,25]. In-vitro and mouse models have

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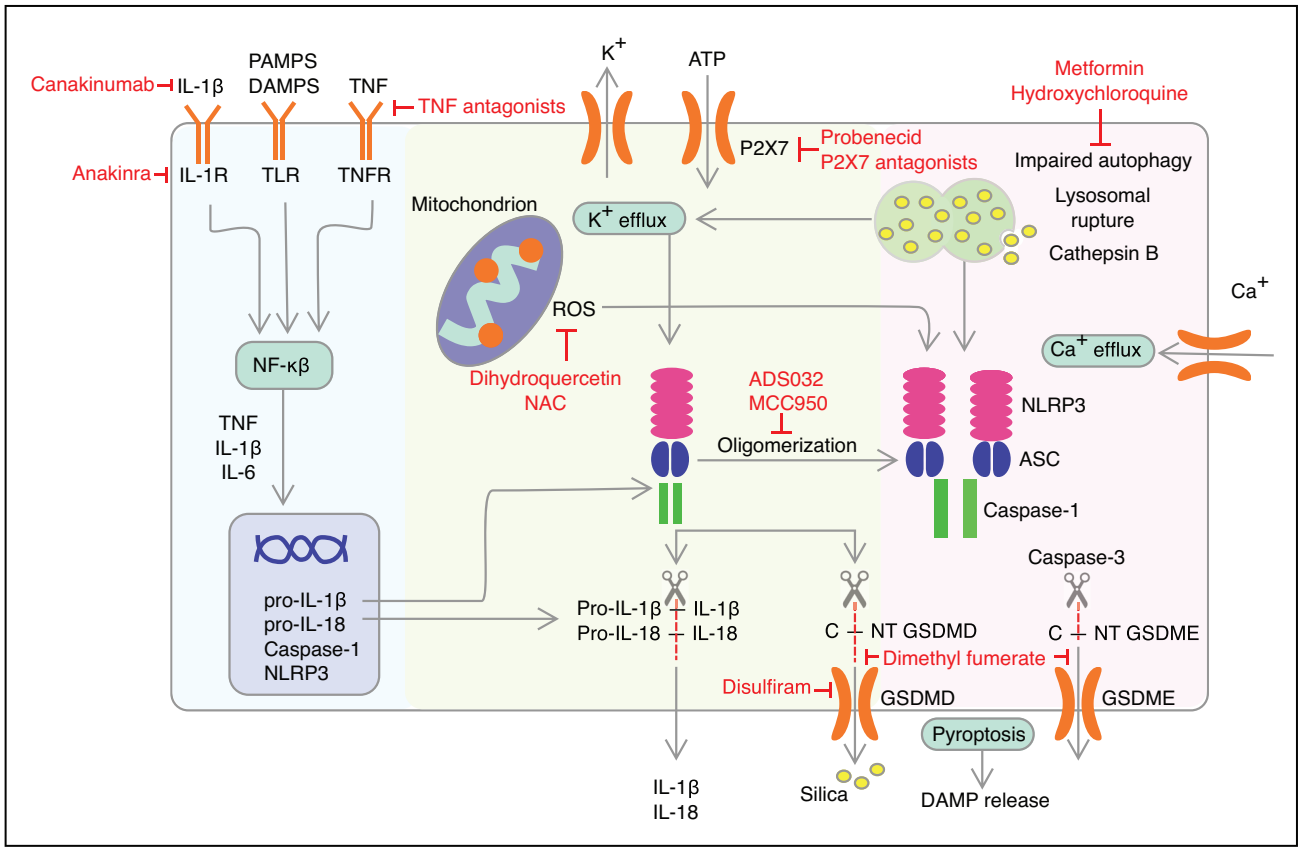

FIGURE 1. Activation of the NLRP3 inflammasome requires two signals to prime and activate the complex. The first signal involves pattern-recognition receptor (PRR)-mediated activation of NF-κB (e.g. TLR-4) and transcription of genes involved in the NLRP3 inflammasome complex, including NLRP3, and pro-caspase-1, as well as cytokines pro-IL-1β and pro-IL-18. A second signal is required for NLRP3 activation, in which NLRP3 binds to apoptosis-associated speck-like protein containing a CARD (ASC), which in turn recruits caspase-1. This causes autocatalysis of pro-caspase-1 to bioactive caspase-1, which subsequently cleaves pro-IL-1β and pro-IL-18. Following assembly of the NLRP3 inflammasome, a second activation signal is required. In silicosis, the second signal includes extracellular ATP activation of the P2X7 receptor (P2X7R), generation of reactive oxygen species (ROS) generated by mitochondrial damage, or lysosomal rupture. Phagocytosed silica particles disrupt the phagolysosomal membrane, allowing acidic hydrolases, including cathepsin B, to leak into the cytosol. Impaired autophagy may also increase the expression of cytokines (TNF, IL-1β, and IL-6) and promote collagen deposition [74]. Caspase-1 activation also leads to cleavage of GSDMD between the autoinhibitory C-terminal and active N-terminal (NT) domains. Active NT GSDMD subunits insert into the lipid membrane and oligomerize to form a transmembrane pore [15]. The GSDMD pore facilitates the release of active pro-inflammatory cytokines IL-1β and IL-18 from macrophages and dendritic cells [16,17]. GSDMD pore formation ultimately leads to osmotic and cell lysis (pyroptosis) and the release of inflammatory cellular contents, including damage-associated molecular patterns (DAMPs) such as IL-1α, ATP, and HMGB1 [75]. Gasdermin E (GSDME) can also be cleaved between its N-terminal and C-terminal domains by caspase-3 during apoptosis to form a pore [21,76▪]. Sites of actions of compounds studied in silicosis are depicted.

demonstrated therapeutic efficacy (Table 1), but a phase II trial in rheumatoid arthritis was ceased early because of abnormal liver enzyme function (unpublished data) [26]. Further clinical trials, including those with inhaled preparations, are ongoing [27▪▪].

Another potential therapeutic target of inflammasomes is the purinergic ionotropic receptor (P2X7R). Probenecid was first used in World War II to extend the limited supply of penicillin and is now a Food and Drug Administration (FDA)-approved drug currently used as an oral treatment for gout with a long and well documented safety profile [28]. Importantly, probenecid inhibits NLRP3 responses *in vitro* and in the lung in murine models [29] and is under investigation as a possible therapeutic in silicosis. Several compounds have been identified as inhibitors of GSDMD alone or both GSDMD and GSDME; however, they have been

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Table 1. Compounds directed at the inflammasome

Compound	Target	Evidence
MCC950	Inhibits NLRP3-mediated oligomerization and subsequent inflammasome assembly	Inhibition of NLRP3 inflammasome activation in silica-treated human bronchial epithelial cells treated with MCC950 compared with untreated control cells [41]. Reduced lung granuloma formation on lung tissue in mice [26,35]
ADS032	Dual NLRP1 and NLRP3 inhibitor	Reduced secretion and maturation of IL-1β in human-derived macrophages and bronchial epithelial cells, and reduced IL-1β and TNF levels in mice [36].
Probenecid	Inhibits the P2X7R leading to reduced NLRP3 inflammasome responses	Reduced secretion and maturation of IL-1β in silica-treated murine macrophages and reduction in airway IL-1β, TNF and IL-6 in mice [29].
Dimethyl fumarate	Inhibits GSDMD and GSDME	Reduction in pyroptosis and IL-1β and IL-18 secretion in mice [37].
Disulfiram	Inhibit GSDMD activation	Improved lung function and histopathological fibrosis in mice [38].

GSMD/E, gasdermin D/E; IL, interleukin; NLRP3, nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3; P2X7R, purinergic ionotropic receptor; TNF, tumor necrosis factor.

shown to have limited specificity [30–34]. These include FDA-approved drugs dimethyl fumarate and disulfiram (Fig. 1 and Table 1).

DOWNSTREAM INFLAMMATION AND FIBROSIS RESULTS FROM MULTIPLE EFFECTOR CELLS AND CYTOKINES

Repeated silica exposure augments chronic activation of inflammasomes and subsequent maturation and release of IL-1β and IL-18 [13] which attract Th1 lymphocytes, Th2 lymphocytes, and type 2 effector cells including eosinophils, mast cells, and fibroblasts [39▪▪] (Fig. 2). TGFβ and IL-6 contribute to the differentiation of Th17 lymphocytes, which are upregulated in silicosis, where they promote the formation of granulomas via the production of IL-17 [40] (Fig. 2). Permanent lung fibrosis and airway remodeling is driven by the pro-fibrotic mediator transforming growth factor beta (TGFβ), a key effector of collagen deposition and turnover in fibrotic lung diseases.

IL-1β also plays a key role in the progression of fibrosis by facilitating Th17 activity [42] and enhancing TGFβ responses [43,44]. In a silicosis mouse model, increased Th17 responses and inflammation were inhibited by the IL1 receptor (IL-1R) antagonist, anakinra, suggesting that effects exerted by Th17 may be dependent on IL-1α and/or IL-1β [40]. Additionally, IL1β levels were reduced following treatment with an anti-IL-17 monoclonal antibody, indicating a role for Th17 in mediating IL-1β expression [40]. Although the role of IL-1β in driving silicosis has been well documented [45,46], there are limited studies examining the in-vivo role IL-18 [47]. Clinical studies of patients with silicosis demonstrate that genetic polymorphisms in TNF, IL-1α, and TGFβ confer a higher risk of disease, and plasma levels of TNF, IL-6, and IL-18 are associated with disease severity and the risk of disease progression [48].

ANTI-CYTOKINE THERAPY: BROAD AND SPECIFIC TARGETS

Therapies that target IL-1 family cytokine production or activity could modulate the disease. Monoclonal antibodies against cytokine production or cytokine receptors are used in a wide variety of other diseases. Conversely, genetic deficiency of IL-1β or antibody-mediated neutralization of IL-1β limits disease progression [45,46]. Anakinra, an IL-1R antagonist (IL-1ra), has been studied in silicosis mouse models [40] and in one human case report [49]. IL-1ra treatment of mice was shown to reduce collagenous-containing pulmonary nodules, however, cellular inflammation in the airways was not largely altered, suggesting it may be useful in established fibrosis but less so in reducing inflammation [56]. Conversely, Song *et al.* [40] demonstrated anakinra treatment substantially decreased silica-induced lung inflammation and the Th17 responses. In contrast, administration of an anti-IL-1β monoclonal antibody in mice found reduced numbers of airway macrophages and neutrophils, as well as reduced TGF-β and fibronectin on lung histopathology, and a skewed Th1/Th2 response [45]. Anakinra was also used in a patient with progressive silicosis [49]. After 6 months of treatment, there was an improvement in oxygenation, diffusing capacity for carbon monoxide (DLCO), and radiological improvement on PET scans but not on other lung function parameters (Table 2).

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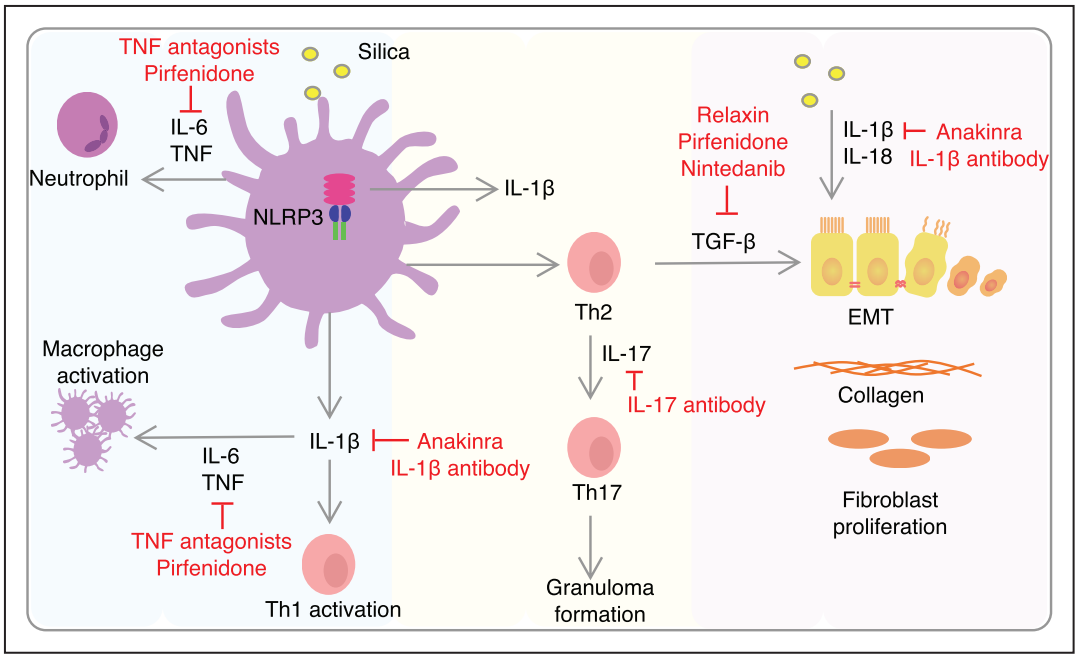

FIGURE 2. IL-1β secreted by macrophages following inflammasome activation induces NF-κB activation and the production of cytokines such as IL-6, TNF, and pro-IL-1β itself, as well as the migration of type 1 alveolar macrophages and neutrophils to the airways. These inflammatory cells attract Th1 lymphocytes, which in turn secrete IFNγ and TNF. Repeated silica exposure augments this inflammatory response, resulting in sustained activation of macrophages that can lead to permanent lung fibrosis and airway remodeling. Fibrosis is driven by the pro-fibrotic mediator transforming growth factor beta (TGFβ), a key effector of collagen deposition and turnover in fibrotic lung diseases. TGFβ and IL-6 contribute to the differentiation of Th17 lymphocytes, which are upregulated in silicosis, where they promote the formation of granulomas via the production of IL-17 [33]. Silica increases the production of IL-1β and IL-18 and induces epithelial–mesenchymal transition (EMT) [77] where epithelial cells acquire a more mesenchymal-like phenotype. EMT promotes further synthesis and deposition of collagen in fibrotic lung diseases, further worsening disease outcomes. Sites of actions of compounds studied in silicosis are depicted.

Anti-TNF drugs have been used for several decades for immune-mediated inflammatory diseases, including rheumatoid arthritis, axial spondylarthritis, psoriasis, and inflammatory bowel disease. Infliximab is the only anti-TNF antagonist studied in silicosis thus far, though it has been used in several other diseases (Table 2). However, caution is advised in the use of TNF antagonists in those with positive autoantibodies, specifically antinuclear antibodies (ANA). This is because of the increased risk of lupus associated with TNF antagonists in these patients. TNF blockade may contribute to defective apoptosis, which in turn could enhance the survival of autoreactive T cells and promote nephritis, as well as resulting in the release of nuclear debris, a trigger for ANA production and lupus [57,58]. Several other cytokine blockade therapies have been studied in mouse models of silicosis, including IL-9, IL-13, and IL-17 (Table 2).

IL-17 receptor antagonists have not yet been studied in humans, but three IL-17 monoclonal antibodies (brodalumab, secukinab, and ixekizumab) are available in clinical practice for psoriasis and other autoimmune diseases. The potential benefits of downregulating or blocking IL-17 should be weighed against the potential risks of increased susceptibility to infections. Common bacterial pathogens *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae,* as well as fungal pathogens including *Pneumocystis carinii* were increased in *Il-17*$^{-/-}$ mice [59]. Patients with silicosis who already have reduced functional parenchyma may not tolerate recurrent or serious pulmonary infections.

Broader immunosuppression strategies have also been studied in silicosis. Prednisolone (30 mg daily for 6 weeks, then tapered to 2.5 mg daily) was studied in 34 patients with silicosis [60]. At 6 months, there was an improvement in FVC% predicted and DLCO% predicted when compared with baseline values. BAL analyses before and after treatment demonstrated a reduction in lymphocyte and total cell counts, and the authors postulated that prednisolone may suppress the alveolitis associated with silicosis. Longer term, larger studies have not

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Table 2. Compounds directed at the immunologic response

Compound	Target	Evidence
Anakinra	IL-1R antagonist	Inhibition of Th17 cytokine activity in mice [40]. One human case report in silicosis – improved oxygenation, DLCO, and PET [49].
Infliximab	Chimeric mouse-human monoclonal antibody which neutralizes TNF	Decreased inflammation and collagen deposition in the lungs, and decreased NF-κB expression of inducible NOS. Improved in lung function and reticulonodular opacities on chest X-ray in sarcoidosis [50].
Etanercept	A 'decoy receptor' fusion protein that inhibits the binding of TNF to its cell surface receptor	Used in RA, psoriasis, IBD. A phase II trial using etanercept in patients with sarcoidosis was stopped early because of a lack of treatment response. A phase II trial in IPF showed a nonsignificant reduction in disease progression [62,51].
IL-9 blockade	IL-9 receptor antagonist targets macrophages, Th2 cells, mast cells, and Th17 cells	Silicosis mice suppressed not only histopathological evidence of fibrosis (hydroxyproline staining) but also reduced type 2 inflammation via IL-12, IL-18, and TNF [52,53].
IL-13 blockade	IL-3 antagonist inhibits granuloma formation, inflammation, and fibrosis	Intranasal administration of an IL-13 recombinant immunotoxin in silica-exposed mice resulted in a reduction in granuloma and collagen deposition, reduction in TNF, TGFβ, and CCL3/MIP-1α and CXCL2/MIP2 BAL concentrations [54].
IL-17	Anti-IL17 monoclonal antibody	Reduction in BAL neutrophils, lymphocytes, and macrophages in silica-exposed mice [40].
Tacrolimus	Calcineurin inhibitor, inhibits T-lymphocytic signal transduction and gene transcription for the cytokines IL-2, IL-3, IL-4, IL-5, GM-CSF, and TNF	In-vitro study demonstrated tacrolimus reduced silica-induced cell proliferation through modulation of the T-cell complex and B-cell complex [55].
Prednisolone	Multiple effector cells and cytokines	Improvement in lung function and reduction in BAL lymphocyte and total cell counts in humans [60].

BAL, bronchoalveolar lavage; CCL3, chemokine ligand 3; CXCL, chemokine CXC ligand-1; DLCO, diffusing lung capacity for carbon monoxide; IBD, inflammatory bowel disease; IL, interleukin; IPF, idiopathic pulmonary fibrosis; NF-κB, nuclear-factor kappa light chain enhancer of activated B cells; NOS, nitric oxide species; RA, rheumatoid arthritis; TGF, transforming growth factor; TNF, tumor necrosis factor.

been conducted. The use of prednisolone in those without alveolitis has not been adequately studied.

ALL PATHS LEAD TO FIBROSIS

Repeated inflammation leads to the recruitment of inflammatory cells and the production of pro-inflammatory and pro-fibrotic cytokines, including IL-1β, IL-18, TNF, and TGFβ. Proliferation of fibroblasts and induction of epithelial–mesenchymal transition, whereby epithelial cells transition to a mesenchymal phenotype, increase the deposition of extracellular matrix containing collagen, fibronectin, and proteoglycans [61] (Fig. 2).

ANTIFIBROTIC THERAPY

Oral antifibrotic drugs, including pirfenidone and nintedanib, now form part of the standard of care in other progressive fibrosing lung diseases [62]. There is an ongoing clinical trial using nintedanib in patients with pneumoconiosis [63]. Other tyrosine kinase inhibitors, including dasatinib and ponatinib, have demonstrated a reduction in lung inflammation and fibrosis in mouse silicosis models [64,65]. However, somewhat conflictingly, tyrosine kinase inhibitors may activate the NLRP3 inflammasome, as demonstrated in in-vitro studies of myeloid cells [66] (Table 3). This suggests further research is required in this area.

Pirfenidone has antifibrotic (reduced collagen synthesis and production of TGFβ and PDGF), anti-inflammatory (reduced TNF, IL-1, IL-6, and NLRP3 inflammasome activation), and antioxidant effects (reduced the production of ROS) [70]. Several mouse studies have demonstrated attenuation of silica-induced inflammation and fibrosis using pirfenidone by inhibition of epithelial–mesenchymal transition via the NLRP3 inflammasome and JAK/STAT pathways [71,72].

Anti-TGFβ drugs have also been studied. Relaxin, a hormone involved in the remodeling of

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Table 3. Compounds directed at the fibrotic response

Compound	Target	Evidence
Nintedanib	Intracellular tyrosine kinase inhibitor that inhibits activation of FGF-R, PDGF-R, VEGF-R	Ongoing clinical trial using nintedanib in patients with pneumoconiosis [63] Reduces lung function decline in IPF and PF-ILDs [67,68]
Dasatinib and ponatinib	Tyrosine kinase inhibitor	Reduction in granuloma formation and in TNF, IL-1β, and TGFβ, and collagen production, increase in M2 macrophages in silica-exposed mice [64,65].
Pirfenidone	Reduces collagen synthesis and production of TGFβ and PDGF, reduces TNF, IL-1, IL-6, and NLRP3 activation, antioxidant	Attenuation of silica-induced inflammation and fibrosis using pirfenidone by inhibition of epithelial–mesenchymal transition via the NLRP3 inflammasome and JAK/STAT pathways [70–72]
Relaxin	RxFP1 receptor agonist educes TGFβ production and targets the NLRP3 inflammasome via caspase-1	Reduces TGFβ and fibroblasts *in vitro* [73,74,69]

FGF-R, fibroblast growth factor receptor; IL, interleukin; JAK/STAT, janus kinases, signal transducer and activator of transcription proteins; NLRP3, nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3; PDGF-R, platelet-derived growth factor receptor; TGF, transforming growth factor; TNF, tumor necrosis factor; VEGF-R, vascular endothelial growth factor receptor.

the extracellular matrix of the female reproductive tract to facilitate parturition, is also an antifibrotic, by reducing TGFβ production. In-vitro studies suggest relaxin reduces fibrosis mediated by TGFβ and fibroblasts [73,74].

AUTOPHAGY

Autophagy is a process by which cells sequester intracellular constituents that are delivered to lysosomes for degradation and recycling of macromolecules [75]. Uptake of silica particles by alveolar macrophages can alter autophagy responses, which has been shown to play a role in silicosis [76▪]. There is also considerable cross-talk between pathways involved in autophagy and cytokines. Autophagy is modulated by AMP-activated protein kinase (AMPK). The AMP-signaling pathway coordinates the induction of autophagy by inhibiting the mammalian target of rapamycin (mTOR pathway). AMPK is also a key player in fibrogenesis by regulating inflammatory injury (via TGFβ), activation, proliferation, and migration of effector cells (myofibroblasts, mesenchymal cells), and reducing extracellular matrix production [77]. There is emerging evidence that nanoparticles (i.e. <100 nm) also disrupt normal autophagy processes, leading to lysosomal dysfunction and negative consequences. Artificial stone dust contains a high concentration of ultrafine or nanosilica particles, which may also contribute to silicosis and other silica-associated diseases [78].

TARGETING AUTOPHAGY AND THE MTOR PATHWAY

Several repurposed drugs targeting the mTOR pathway have been studied in murine models of silicosis, including carvedilol, metformin, and hydroxychloroquine [79,80] (Table 4).

OXIDATIVE STRESS

Silica stimulates the respiratory burst in phagocytic cells, with a resultant increase in oxygen consumption and ROS production. Crystalline silica is piezoelectric, that is, it produces opposite electrical charges on opposite sides of the physical structure when force is applied [81,82]. This contributes to the formation of ROS on the cleaved surface of silica particles. The redox potential is even greater with freshly fractured silica. Oxidative stress increases the production of antioxidant enzymes, including manganese superoxide dismutase, glutathione peroxidase, and inducible nitric oxide synthetase. Oxidant production activates cell signaling pathways, including NLRP3 [83], MAP/ERK kinase and ERK phosphorylation [81], and increases the expression NF-κB and AP-1-dependent cytokines. Serum superoxide dismutase, malondialdehyde, and glutathione are increased in those with silicosis [82,84].

ANTI-OXIDANT THERAPY

Accumulation of ROS and lipid peroxidation can lead to ferroptosis, a novel type of programmed cell death that occurs in silicosis. Ferroptosis is regulated by glutathione, among other factors. It is also closely linked to autophagy [85▪]. Dihydroquercetin, a flavonoid, demonstrated a reduction in silica-induced inflammation *in vitro* and in mouse models by inhibiting ferroptosis (Table 4).

N-acetylcysteine (NAC) is a tripeptide precursor of glutathione and has postulated antioxidant properties as a scavenger of ROS and inhibitor of

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Table 4. Drugs directed at autophagy and oxidation

Drug	Target	Evidence
Carvedilol	Nonselective α/β adrenoceptor blocker	Reduced silica-induced increases in lung protein levels of protein kinase B (P-AKT) and mTOR, and hydroxyproline [79]
Metformin	Activates autophagy via the AMPK-mTOR signaling pathway	Reduced collagen deposition and lung α-SMA concentration in silica-exposed mice [86]
Hydroxychloroquine	Blocks lysosomal membrane permeability	Reduces activation of the NLRP3 inflammasome in silica-exposed mice [80]
Dihydroquercetin	Inhibits ferroptosis via a reduction in iron and lipid peroxidation products and increased glutathione	Reduction in inflammation *in vitro* and in silica-exposed mice. Reduced fibrosis by modulating the PI3K/AKT/mTOR and TGFβ/Smad pathways in mice of liver fibrosis [85▪,87]
NAC	Glutathione precursor, ROS scavenger, cyclo-oxygenase-2 inhibitor	Retrospective study of 70 silicosis patients treated with NAC and tetrandine (a Chinese medicine-derived calcium antagonist) found an improvement in exercise tolerance but not lung function in the treated compared with the untreated group [89]

α-SMA, alpha smooth muscle actin; AMPK, adenosine monophosphate-activated protein kinase; MPO, myeloperoxidase; mTOR, mammalian target of rapamycin; NAC, n-acetylcysteine; NLRP3: nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3; P-AKT, phosphorylated AKT; PI3K, plasma membrane-associated lipid kinases; TGFβ, transforming growth factor β.

cyclo-oxygenase-2 and membrane lipid peroxidation (Fig. 1). In other pulmonary fibrosis models, NAC reduced pro-inflammatory cytokines, reduced ROS and mitochondrial apoptosis signaling, and reduced lung fibrosis [88]. Mouse models found a reduction in inflammation and fibrosis (via a reduction in E-cadherin), and a reduction in MDA (an indicator of antioxidant stress) [88]. A retrospective study of 70 silicosis patients treated with combined NAC and tetrandine (a Chinese medicine-derived calcium antagonist) found an improvement in 6MWD but not in pulmonary function tests in the treated group compared with the untreated group [89]. However, the efficacy and safety of NAC in other forms of pulmonary fibrosis (i.e. IPF) are conflicting. The PANTHER-IPF study, which examined NAC plus azathioprine plus prednisolone compared with placebo, was stopped early because of increased mortality in the combination treatment arm [90]. Post hoc analyses suggested that those with short telomere length were more likely to experience adverse events [91]. In contrast, those with the rs3750920 TT genotype had a reduced risk of disease progression with treatment, which led to the PRECISIONS trial, which aims to treat this specific genotype with NAC [92]. Therefore, further research into the efficacy and risk of NAC in patients with silicosis is required.

CONCLUSION

Given all that we understand thus far about the pathogenesis of silicosis and the variable success of multiple therapies trialed mostly *in vitro* and in mouse models, what is the best treatment for silicosis? The answer, frustratingly, is likely that there is no silver bullet; silicosis is a complex disease, and the answer might be that it requires a multimodal approach. Unlike other diseases, down-regulation of the immune system may not be enough because silica particles will remain in the lung parenchyma and can exert damage via additional nonimmunological pathways. It may be that a combination of silica clearance treatments, such as whole lung lavage, in combination with immunosuppression, antioxidants, autophagy modulation, or other therapies is the ideal approach. Which therapies for each of these targets should be used? An immunosuppressant that targets IL-1, IL-17, TNF, and TGF and has anti-inflammatory and antifibrotic effects with the least chance of unwanted side effects is likely to be most efficacious. There is considerable cross-talk between pathways; agents that modulate both inflammation, fibrosis, autophagy, and ROS production are ideal.

What are the challenges to finding a cure?

Silicosis is a heterogeneous disease. The degree of parenchymal involvement and risk of progression vary considerably among patients. It can be difficult to determine who will be rapidly progressive and in whom treatment with potential for side effects may be warranted, versus who will be stable or only slowly progressive following exposure cessation, and in whom the risk of adverse events may not outweigh the benefit. We, therefore, need more accurate markers of disease progression. Furthermore, traditional markers of parenchymal lung disease, such as lung function testing, may not accurately reflect the degree of impairment in these patients.

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In addition, the potential adverse effects of the therapies described are very relevant to the silicosis cohort. Therapies that modulate macrophage phagocytosis increase the risk of tuberculosis reactivation, a common comorbidity in the silicosis population. Some immunosuppressants increase the risk of autoimmunity, the risk of which is already increased in the silicosis population. How long should patients be treated for? Those now diagnosed with silicosis tend to be much younger, and long-term use of these treatments may increase the risk of side effects. The potential efficacy of many therapies has only thus far been studied in the mouse models of silicosis, which do recapitulate the disease seen in humans. There are many challenges in translating animal studies to the complexity of humans. However, as the rate of accelerated silicosis is rising, now is the time to push cautiously forward with human trials of treatments for silicosis.

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Conflicts of interest

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

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